

**Official Title:** A MULTICENTER, OPEN-LABEL, PHASE III STUDY TO  
EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS,  
AND PHARMACODYNAMICS OF EMICIZUMAB GIVEN EVERY 4  
WEEKS (Q4W) IN PATIENTS WITH HEMOPHILIA A

**NCT Number:** NCT03020160

**Document Date:** PROTOCOL

Version 3: 25 July 2017

## PROTOCOL

**TITLE:** A MULTICENTER, OPEN-LABEL, PHASE III STUDY  
TO EVALUATE THE EFFICACY, SAFETY,  
PHARMACOKINETICS, AND  
PHARMACODYNAMICS OF EMICIZUMAB GIVEN  
EVERY 4 WEEKS (Q4W) IN PATIENTS WITH  
HEMOPHILIA A

**PROTOCOL NUMBER:** BO39182

**VERSION NUMBER:** 3

**EUDRACT NUMBER:** 2016-001094-33

**IND NUMBER:** 122954

**TEST PRODUCT:** Emicizumab (RO5534262)

**MEDICAL MONITOR:** [REDACTED], Ph.D.

**SPONSORS:** F. Hoffmann-La Roche Ltd  
Chugai Pharmaceutical Co. Ltd.

**DATE FINAL:** Version 1: 24 March 2016

**DATE AMENDED:** Version 2: 19 November 2016  
Version 3: See electronic date stamp below.

## PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[REDACTED]	Company Signatory (Clinical)	25-Jul-2017 15:12:50

### CONFIDENTIAL

F. Hoffmann-La Roche Ltd of Basel, Switzerland, and Chugai Pharmaceutical Co. Ltd.\* of Tokyo, Japan, will act as co-sponsors of this global study. However, it may be implemented in individual countries by Roche's local affiliates, including Genentech, Inc. in the United States, or Chugai Pharmaceutical Co. Ltd.\* in South Korea, Taiwan, and Japan. The information contained in this document, especially any unpublished data, is the property of F. Hoffmann-La Roche Ltd (or under its control) and therefore is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Roche except to the extent necessary to obtain informed consent from persons to whom the drug may be administered.

\*Chugai will act as the Sponsor only in South Korea, Taiwan, and Japan. The specific details of the legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

**Emicizumab—F. Hoffmann-La Roche Ltd**  
Protocol BO39182, Version 3

## **PROTOCOL AMENDMENT, VERSION 3: RATIONALE**

Protocol BO39182, Version 3, has been amended to include new safety findings of thrombotic microangiopathy (TMA) in Study BH29884 and ways to mitigate those findings. Changes to the protocol, along with a rationale for each change, are summarized below:

- Update on safety findings of TMA observed in Study BH29884 has been added (Sections 1.2.2, 1.3, 3.1.2, 5.1.2.3, and 5.1.2.4).
- Language has been revised to clarify that the safety follow-up visit will be performed after 24 weeks for patients who discontinue emicizumab treatment (Section 3.2).
- An inclusion criterion has been updated for patients without factor VIII (FVIII) inhibitors, and FVIII inhibitor titer cutoff has been specified for patients for whom the inhibitor titer was measured in laboratories with an historical reduced sensitivity for inhibitor detection (Sections 3.3.2 and 4.1.1).
- Information about administration of emicizumab for patients on 6 mg/kg every 4 weeks who miss a dose has been included (Section 4.3.2.1).
- An exception has been added for patient's ability to self-administer study drug on days when pharmacokinetic (PK) assessment is planned. Emicizumab should be administered at the investigational site when PK samples are to be collected (Section 4.3.2.1).
- Clarification on activated prothrombin complex concentrate (aPCC) use has been added: Use of aPCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds (Section 4.4.1).
- Clarification about anti-fibrinolytics use has been added: Anti-fibrinolytics in combination with recombinant activated factor VII are to be used with caution (Section 4.4.1) and are to be avoided in combination with aPCC or Byclot<sup>®</sup> (Section 4.4.2).
- Language has been modified regarding the prohibited use of drugs that would affect hemostasis to specify non-steroidal anti-inflammatory drugs that are not selective or preferential COX-2 inhibitors (Section 4.4.2).
- Clarification regarding laboratory monitoring of coagulation status after any bypassing agent use has been added. Laboratory monitoring is to be done after any use of a bypassing agent and not only after use of a bypassing agent to treat breakthrough bleeds (Sections 4.5.5 and 5.1.3, Appendix 1).
- Information about where to record laboratory results for patients who require multiple doses of bypassing agents has been updated to Treatments with Bypassing Agents electronic Case Report Form (Section 4.5.5. and Appendix 2).

- Definition of "joint bleeds" has been modified from the International Society on Thrombosis and Haemostasis definition because of lack of clarity. The previous definition of "joint bleed" required the reporting of a combination of an "unusual sensation (aura) in the joint" and another joint bleed symptom (e.g., decreased range of motion) as per the bleed/medication questionnaire. The definition of "joint bleed" was redefined as follows:

Bleeds with bleed type "joint bleed" reported with at least one of the symptoms of joint bleed as per the questionnaire except for the symptom "unusual sensation (aura) in the joint" reported alone (Section 4.5.8).

- New safety risk associated with emicizumab has been added as follows:

Life- threatening bleeding due to unreliable standard coagulation tests and inhibitors assays in the setting of emicizumab.

Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and are impacted by the presence of emicizumab and, therefore, are not reflecting the patient's underlying hemostatic status accurately (Section 5.1.2.5).

- Following the request from one health authority after Clinical Trial Application review, the statistical section has been updated with the statement that a sample size of 40 patients is expected to provide statistically robust point estimates and meaningfully narrow confidence intervals. This statement is to provide additional justification for the sample size of 40 patients which is primarily based on clinical considerations (Section 6.1).
- Axillary temperature measurement was added as an additional option for body temperature measurement (Appendix 1).
- Clarification has been made that the safety follow-up visit will be performed after 24 weeks, with a deviation of +7 days being acceptable (Appendix 1).
- Safety laboratory testing following up-titration of emicizumab has been added (Appendix 1).

The protocol has been modified to reflect updates to the protocol template in the following sections:

- The protocol has been modified to prohibit use of the term "sudden death" on the Adverse Event eCRF, unless it is combined with the presumed cause of death (e.g., "sudden cardiac death"), as use of the term "sudden death" will require the Sponsor to query the site for clarification on the cause of death (Section 5.3.5.8).
- Section 5.3.5.11 has been modified to clarify the reporting of adverse events leading to hospitalization.
- Language has been added to clarify that the Sponsor will review all protocol deviations as per the Sponsor's Standard Operating Procedures, and prospective requests to deviate from the protocol are not allowed (Section 9.2).

- The Web site URL for the "Roche Global Policy on Sharing of Clinical Trials Data" has been corrected (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

## PROTOCOL AMENDMENT, VERSION 3: SUMMARY OF CHANGES

### PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

#### **SECTION 1.2.2: Clinical Experience**

As of ~~October~~ April 2017~~6~~, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), thrombotic microangiopathy (TMA); ~~atypical hemolytic uremic syndrome (aHUS)~~ was observed in 32 patients receiving emicizumab and bypassing agents; and 2 cases of thromboembolic events were observed in 2 patients receiving emicizumab and bypassing agents. For more details, refer to Sections 5.1.2.3 and 5.1.2.4.

#### **SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT**

Emicizumab was well tolerated in the Phase I/II studies. The majority of adverse events were of mild intensity, with the most common being injection-site reactions. The majority of the adverse events were not considered related to emicizumab. In these studies, no thromboembolic or systemic hypersensitivity adverse events were observed; however, in the ongoing Phase III Study BH29884, 32 cases of TMA (~~aHUS~~) and 2 thromboembolic events were observed in patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds. Three out of these 54 patients have fully recovered, ~~and the fourth~~ while 1 patient's condition has improved *and 1 patient has died due to severe rectal bleeding* (see Sections 5.1.2.3 and Section 5.1.2.4).

#### **SECTION 3.1.2: Expansion Part**

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). There is clinical experience in the ongoing Phase I/II clinical studies with the treatment of over 60 breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents. FVIII, aPCC, or rFVIIa do not interfere with emicizumab PK assessments and no safety signals have been observed when breakthrough bleeds were treated with standard-of-care regimens during Phase I/II studies. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 2-3 events of TMA and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see Sections 5.1.2.3 and 5.1.2.4). Therefore, it is recommended that breakthrough bleeds in the inhibitor population are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided ~~or limited~~ (see Section 4.4.1). *In addition, caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients who are receiving emicizumab, and the use of anti-fibrinolytics is prohibited in conjunction with aPCC or Byclot® (see Sections 4.4.1 and 4.4.2)....*

Breakthrough bleeds will be treated with appropriate coagulation products with either FVIII (non-inhibitor patients) or rFVIIa (inhibitor patients) at the lowest expected dose to achieve hemostasis and captured as they occur (see Section 4.4.1). When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use of coagulation products (e.g., FVIII or rFVIIa) will be documented (e.g., bleeding, preventative dose before activity). Thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. For patients with inhibitors against FVIII who *receive* ~~experience a breakthrough bleed that requires treatment with~~ bypassing agents, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see Appendix 1 and Appendix 2).

## **SECTION 3.2: END OF STUDY AND LENGTH OF STUDY**

The length of the study for an individual patient will be:

- *For patients who discontinue emicizumab treatment, safety follow-up visit 24 weeks after discontinuing emicizumab* ~~unless patient transfers to a separate emicizumab extension study~~

### **SECTION 3.3.2: Rationale for Patient Population**

Although the severity of a patient's hemophilia A is directly related to the FVIII activity, inter-patient variability may exist based on level of physical activity, bleeding history, and other features. Therefore, patients previously treated with episodic FVIII or bypassing agents will be required to have at least 5 bleeds in the last 24 weeks prior to study entry to be eligible for enrollment into the expansion cohort. This requirement is intended to select a group of patients with hemophilia A who have a high, unmet medical need and to enable evaluation of adequate control of bleeding in this population. Patients who have been on previous prophylactic treatment can enroll (in the expansion phase only) without any requirement for a certain bleed number because these patients' bleeds should be well controlled through receiving their current standard of care. In order to exclude patients who might have a higher chance to show an immune response to foreign protein regimens (e.g., FVIII), patients without FVIII inhibitors ( $<0.6$  BU/mL;  $<1.0$  BU/mL *only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL*) who completed successful immune tolerance induction (ITI) at least 5 years before screening must have no evidence of inhibitor recurrence (permanent or temporary), indicated by detection of an inhibitor, FVIII half-life  $<6$  hours, or FVIII recovery  $<66\%$  since ITI (Antun et al. 2015).

### **SECTION 4.1.1: Inclusion Criteria**

Patients must meet the following criteria for study entry:

- Patients without FVIII inhibitors (<0.6 BU/mL; < 1.0 BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL) who completed successful ITI must have done so at least 5 years before screening and must have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor >0.6 BU/mL (> 1.0 BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL) since ITI (Antun et al. 2015)

### **SECTION 4.3.2.1: Subcutaneous Emicizumab**

The emicizumab regimen being tested is 3 mg/kg QW for 4 weeks followed by 6 mg/kg Q4W subcutaneously for 24 weeks. *For patients on 6 mg/kg Q4W who missed a dose, emicizumab should be administered as soon as possible but no later than 14 days from planned administration day. If more than 14 days have passed, the patient should take the next dose of emicizumab at the next scheduled date. In all cases, the study medication dosing will proceed in accordance with the original dosing schedule....*

For patients in the PK run-in cohort, all drug administrations in Weeks 1–25 will be conducted at the investigational site by an HCP. Patients who remain in the study after Week 25 will have the option to self-administer emicizumab at home if patient's ability to self-administer the study drug is documented in the source data, *except on days when PK assessment is planned (see Appendix 2). On these days, emicizumab should be administered at the investigational site after the PK sample has been drawn.*

Patients in the expansion cohort will also need to come to the site at all times of drug administration in Weeks 1–25 because predose PK and PD samples have to be drawn. Therefore, all SC injections will be performed at the site until Week 25 (unless mobile nursing [MN] is implemented; see Section 4.5). However, unassisted self-administration of the drug at the investigational site will be supported for patients in the expansion cohort, and patients remaining in the study after Week 25 might have the option to self-administer emicizumab at home. *On days when PK samples are to be collected (see Appendix 2), emicizumab should be administered at the investigational site after the PK sample has been drawn.*

### **SECTION 4.4.1: Permitted Therapy**

Concomitant use of the following drugs and therapies will be permitted:

- Drugs intended to control bleeds, including FVIII concentrates (non-inhibitor patients) or rFVIIa (inhibitor patients), should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve hemostasis may be lower than the FVIII or bypassing agent doses used prior to starting the study....



*Use of aPCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed with no more than 50 units/kg of aPCC to be administered as an initial dose. For patients receiving aPCC prior to study entry, a washout period of 72 hours prior to first emicizumab dosing is required....*

- *Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab.*

#### **SECTION 4.4.2: Prohibited Therapy**

Use of the following therapies is prohibited for at least 4 weeks prior to initiation of study treatment, during the study, and until last observation (except for aPCC and Byclot that require a washout period of 72 hours prior to study treatment and it can be used for the treatment of breakthrough bleeds during the study as per guidance in Section 4.4.1):

- Drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs *that are not selective or preferential COX-2 inhibitors*, or anticoagulants [other than to flush, dwell, or de-clot a venous access device]) but excluding drugs intended to control bleeding episodes or used in the context of minor surgery (e.g., tooth extraction) or injuries (e.g., concussion) to prevent deterioration...
- *Use of anti-fibrinolytics in conjunction with aPCC or Byclot*

#### **SECTION 4.5.5: Laboratory, Biomarker, and Other Biological Samples**

*In the event of use of a bypassing agent, ~~In the event of a bleed treated with bypassing agents,~~ the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent ~~administration~~ use so the investigator may monitor for ~~of~~ potential thromboembolic events and thrombotic microangiopathy: platelet count, serum creatinine, LDH, and schistocytes. A plasma sample should also be provided for local and central laboratory monitoring of prothrombin fragment 1+2, fibrinogen and D-dimer. If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents ~~administered to treat a given bleed~~. If applicable, laboratory results should be recorded in the *Following Treatment with Bypassing Agents eCRF form*. ~~unscheduled visit eCRFs.~~*

The following samples will be sent to the Sponsor or a designee for centralized analysis:

- Plasma for PD and exploratory PD biomarker assessments (aPTT, PT, FVIII activity, thrombin generation, FIX:Ag, FX:Ag, and others as listed in Appendix 2).
- *Plasma aliquot for central lab assessment of fibrinogen, D dimer, and prothrombin fragment 1.2, collected after administration of bypassing agents (as*

*listed in Appendix 1, Schedule of Assessments, in the footnotes). This sample is addition to the local laboratory monitoring after bypassing agent use as described above.*

#### **SECTION 4.5.8: Bleed Definitions**

##### **Definitions of Bleed Sites**

- Joint bleeds (~~other joints except target joints~~) are defined as bleeds with bleed type “joint bleed” reported via the bleed/medication questionnaire ~~an unusual sensation (“aura”) in the joint, in combination with at least one any of the following symptoms:~~

#### **SECTION 5.1.2.3: Hypercoagulation and Thromboembolic Events**

As of April 2017~~October 2016~~, there have been 2 *serious* thromboembolic events reported in 2 patients with hemophilia A with inhibitors while receiving emicizumab in Study BH29884. [REDACTED]

[REDACTED] ....

#### **SECTION 5.1.2.4: Thrombotic Microangiopathy**

Thrombotic microangiopathy is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, etc. As of ~~October~~ April 2017~~6~~, 2-3 cases of TMA, ~~diagnosed as aHUS~~, were observed in a Phase III clinical study involving patients with hemophilia A with inhibitors while receiving emicizumab. [REDACTED]

[REDACTED] ....

[REDACTED]

Brochure.

*For more details please refer to Investigator*

### **SECTION 5.1.2.5: Life-Threatening Bleeding Due to Unreliable Standard Coagulation Tests and Inhibitor Assays in the Setting of Emicizumab**

*Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis (see Section 5.1.4). Due to the long t<sub>1/2</sub> of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose.*

*There is a risk of life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab in the market setting by practitioners, particularly for emergency care practitioners.*

*Emicizumab's mechanism of action and resulting interference was clearly demonstrated in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials also demonstrated the effects of emicizumab on laboratory tests. However, as of April 2017, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab were observed.*

### **TABLE 1: Guidelines for Management of Specific Adverse Events**

Table 1 has been clarified regarding laboratory monitoring of coagulation status after the use of any bypassing agent.

### **SECTION 5.3.5.8: Deaths**

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

#### **SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization**

*An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event: ~~The following hospitalization scenarios are not considered to be adverse events:~~*

*An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead. ~~The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:~~*

#### **SECTION 6.1: DETERMINATION OF SAMPLE SIZE**

The overall sample size of 40 patients in the expansion cohort is based primarily on clinical considerations taking into account the limited number of patients with hemophilia A. ~~It is expected that a~~ *A sample size of 40 patients would be expected to, nonetheless, provide statistically robust point estimates with meaningfully narrow confidence intervals.*

#### **SECTION 9.2: PROTOCOL DEVIATIONS**

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

#### **SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS**

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

*[http://www.roche.com/roche\\_global\\_policy\\_on\\_sharing\\_of\\_clinical\\_study\\_information.pdf](http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf)*

<http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf>

#### **APPENDIX 1: Schedule of Assessments**

The schedule of assessments has been revised to reflect the changes to the protocol.

## **APPENDIX 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples**

Appendix 2 has been updated so that laboratory results for patients who require multiple doses of bypassing agents are recorded to the Treatments with Bypassing Agents electronic Case Report Form.

## TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM .....	19
PROTOCOL SYNOPSIS .....	20
1. BACKGROUND .....	31
1.1 Background on Hemophilia A .....	31
1.1.1 Management.....	31
1.2 Background on Emicizumab .....	34
1.2.1 Molecule and Preclinical Data .....	34
1.2.2 Clinical Experience .....	35
1.3 Study Rationale and Benefit-Risk Assessment.....	39
2. OBJECTIVES AND ENDPOINTS .....	40
2.1 Pharmacokinetic Run-In Phase .....	40
2.1.1 Objectives.....	40
2.2 Expansion Phase.....	40
2.2.1 Efficacy Objectives .....	40
2.2.2 Safety Objectives.....	41
2.2.3 Pharmacokinetic Objective .....	41
2.2.4 Exploratory Pharmacodynamic Biomarker Objective.....	41
3. STUDY DESIGN .....	41
3.1 Description of the Study.....	41
3.1.1 PK Run-In Part .....	41
3.1.2 Expansion Part .....	42
3.2 End of Study and Length of Study .....	45
3.3 Rationale for Study Design .....	46
3.3.1 Rationale for Emicizumab Dose and Schedule.....	46
3.3.2 Rationale for Patient Population .....	48
3.3.3 Rationale for Biomarker Assessments.....	49
3.3.4 Rationale for Patient-Reported Outcome Assessments .....	50
4. MATERIALS AND METHODS .....	50

4.1	Patients.....	50
4.1.1	Inclusion Criteria.....	50
4.1.2	Exclusion Criteria.....	52
4.2	Method of Treatment Assignment.....	53
4.3	Study Treatment.....	53
4.3.1	Formulation, Packaging, and Handling.....	53
4.3.2	Dosage, Dose Adjustments, Administration, and Compliance.....	54
4.3.2.1	Subcutaneous Emicizumab.....	54
4.3.3	Investigational Medicinal Product Accountability.....	55
4.3.4	Post-Study Access to Emicizumab.....	56
4.4	Concomitant Therapy.....	56
4.4.1	Permitted Therapy.....	57
4.4.2	Prohibited Therapy.....	58
4.5	Study Assessments.....	58
4.5.1	Informed Consent Forms and Screening Log.....	59
4.5.2	Medical History and Demographic Data.....	59
4.5.3	Physical Examinations.....	59
4.5.4	Vital Signs.....	60
4.5.5	Laboratory, Biomarker, and Other Biological Samples.....	60
4.5.5.1	Pharmacokinetic Samples.....	61
4.5.6	Electrocardiograms.....	62
4.5.7	Patient-Reported Outcomes.....	62
4.5.8	Bleed Definitions.....	64
4.6	Patient, Treatment, Study, and Site Discontinuation.....	65
4.6.1	Patient Discontinuation.....	65
4.6.2	Study Treatment Discontinuation.....	66
4.6.3	Study and Site Discontinuation.....	66
5.	ASSESSMENT OF SAFETY.....	66
5.1	Safety Plan.....	66
5.1.1	Patient Selection.....	67
5.1.2	Risks Associated with Emicizumab.....	67

5.1.2.1	Injection-Site Reactions .....	67
5.1.2.2	Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction .....	67
5.1.2.3	Hypercoagulation and Thromboembolic Events .....	68
5.1.2.4	Thrombotic Microangiopathy .....	68
5.1.2.5	Life-Threatening Bleeding Due to Unreliable Standard Coagulation Tests and Inhibitor Assays in the Setting of Emicizumab .....	69
5.1.3	Management of Specific Adverse Events .....	71
5.1.4	Interpretation of Coagulation Assays for Patients Receiving Emicizumab .....	73
5.2	Safety Parameters and Definitions .....	73
5.2.1	Adverse Events .....	73
5.2.2	Serious Adverse Events (Immediately Reportable to the Sponsor) .....	74
5.2.3	Adverse Events of Special Interest (Immediately Reportable to the Sponsor) .....	75
5.3	Methods and Timing for Capturing and Assessing Safety Parameters .....	75
5.3.1	Adverse Event Reporting Period .....	75
5.3.2	Eliciting Adverse Event Information .....	76
5.3.3	Assessment of Severity of Adverse Events .....	76
5.3.4	Assessment of Causality of Adverse Events .....	76
5.3.5	Procedures for Recording Adverse Events .....	77
5.3.5.1	Injection-Site Reactions .....	77
5.3.5.2	Diagnosis versus Signs and Symptoms .....	77
5.3.5.3	Adverse Events That Are Secondary to Other Events .....	78
5.3.5.4	Persistent or Recurrent Adverse Events .....	78
5.3.5.5	Abnormal Laboratory Values .....	78
5.3.5.6	Abnormal Vital Sign Values .....	79
5.3.5.7	Abnormal Liver Function Tests .....	80
5.3.5.8	Deaths .....	80
5.3.5.9	Preexisting Medical Conditions .....	80
5.3.5.10	Lack of Efficacy or Worsening of Hemophilic Bleeds .....	81



5.3.5.11	Hospitalization or Prolonged Hospitalization.....	81
5.3.5.12	Adverse Events Associated with an Overdose or Error in Drug Administration .....	82
5.3.5.13	Patient-Reported Outcome Data .....	82
5.4	Immediate Reporting Requirements from Investigator to Sponsor .....	82
5.4.1	Emergency Medical Contacts .....	83
5.4.2	Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest .....	83
5.4.2.1	Events That Occur prior to Study Drug Initiation.....	83
5.4.2.2	Events That Occur after Study Drug Initiation.....	83
5.4.3	Reporting Requirements for Pregnancies.....	84
5.4.3.1	Pregnancies in Female Patients .....	84
5.4.3.2	Pregnancies in Female Partners of Male Patients .....	84
5.4.3.3	Abortions .....	84
5.4.3.4	Congenital Anomalies/Birth Defects .....	85
5.5	Follow-Up of Patients after Adverse Events .....	85
5.5.1	Investigator Follow-Up .....	85
5.5.2	Sponsor Follow-Up .....	85
5.6	Adverse Events that Occur after the Adverse Event Reporting Period.....	85
5.7	Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees.....	86
6.	STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN .....	86
6.1	Determination of Sample Size .....	86
6.2	Summaries of Conduct of Study .....	86
6.3	Summaries of Demographic and Baseline Characteristics.....	87
6.4	Efficacy Analyses .....	87
6.4.1	Efficacy Endpoints .....	87
6.4.2	Patient-Reported Outcomes .....	88
6.5	Safety Analyses .....	88
6.6	Pharmacokinetic Analyses.....	88
6.7	Immunogenicity Analyses .....	89

6.8	Exploratory Analyses .....	89
6.9	Interim analysis.....	89
6.9.1	Planned Interim Analysis .....	89
6.9.2	Optional Interim Analysis .....	90
7.	DATA COLLECTION AND MANAGEMENT .....	90
7.1	Data Quality Assurance .....	90
7.2	Electronic Case Report Forms.....	90
7.3	Electronic Patient-Reported Outcome Data.....	90
7.4	Source Data Documentation.....	91
7.5	Use of Computerized Systems .....	92
7.6	Retention of Records .....	92
8.	ETHICAL CONSIDERATIONS.....	92
8.1	Compliance with Laws and Regulations .....	92
8.2	Informed Consent .....	92
8.3	Institutional Review Board or Ethics Committee .....	94
8.4	Confidentiality .....	94
8.5	Financial Disclosure .....	94
9.	STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION .....	95
9.1	Study Documentation .....	95
9.2	Protocol Deviations.....	95
9.3	Site Inspections .....	95
9.4	Administrative Structure.....	95
9.5	Publication of Data and Protection of Trade Secrets .....	96
9.6	Protocol Amendments .....	97
10.	REFERENCES .....	98

## LIST OF TABLES

Table 1	Guidelines for Management of Specific Adverse Events .....	71
Table 2	Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale .....	76

## LIST OF FIGURES

Figure 1	Study Schema.....	43
Figure 2	Simulated Plasma Emicizumab Concentration over Time (Q4W Dosing) .....	48

## LIST OF APPENDICES

Appendix 1	Schedule of Assessments.....	103
Appendix 2	Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples.....	110
Appendix 3	WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events .....	115
Appendix 4	Clinical Criteria for Diagnosing Anaphylaxis.....	122
Appendix 5	Haemo-QoL-SF (United States/English) .....	123
Appendix 6	Haem-A-QoL (United States/English) .....	125
Appendix 7	EQ-5D-5L (United Kingdom/English) .....	132

## PROTOCOL AMENDMENT ACCEPTANCE FORM

**TITLE:** A MULTICENTER, OPEN-LABEL STUDY TO  
EVALUATE THE EFFICACY, SAFETY,  
PHARMACOKINETICS AND  
PHARMACODYNAMICS OF EMICIZUMAB GIVEN  
EVERY 4 WEEKS (Q4W) IN PATIENTS WITH  
HEMOPHILIA A

**PROTOCOL NUMBER:** BO39182

**VERSION NUMBER:** 3

**EUDRACT NUMBER:** 2016-001094-33

**IND NUMBER:** 122954

**TEST PRODUCT:** Emicizumab (RO5534262)

**MEDICAL MONITOR:** [REDACTED], Ph.D.

**SPONSOR:** F. Hoffmann-La Roche Ltd  
Chugai Pharmaceutical Co. Ltd.

**I agree to conduct the study in accordance with the current protocol.**

---

Principal Investigator's Name (print)

---

Principal Investigator's Signature

---

Date

Please retain the signed original of this form for your study files. Please return a copy to your local study monitor.

## PROTOCOL SYNOPSIS

**TITLE:** A MULTICENTER, OPEN-LABEL, PHASE III STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF EMICIZUMAB GIVEN EVERY 4 WEEKS (Q4W) IN PATIENTS WITH HEMOPHILIA A

**PROTOCOL NUMBER:** BO39182

**VERSION NUMBER:** 3

**EUDRACT NUMBER:** 2016-001094-33

**IND NUMBER:** 122954

**TEST PRODUCT:** Emicizumab (RO5534262)

**PHASE:** Phase III

**INDICATION:** Hemophilia A

**SPONSOR:** F. Hoffmann-La Roche Ltd  
Chugai Pharmaceutical Co. Ltd.

### **Objectives and Endpoints**

#### **Pharmacokinetic Run-In Phase Objectives**

The objectives of the pharmacokinetic run-in are as follows:

- To investigate the pharmacokinetics of emicizumab after single and multiple (every 4 weeks [Q4W]) subcutaneous (SC) administration of 6 mg/kg
- To assess the safety and tolerability of emicizumab after Q4W SC administration of 6 mg/kg
- To explore the prophylactic effect of emicizumab in maintaining adequate control of bleeding
- To investigate the effect of emicizumab on pharmacodynamic (PD) markers including (but not limited to) aPTT, thrombin generation, and factor VIII (FVIII) activity

#### **Expansion Phase**

##### **Efficacy Objectives**

The efficacy objectives are as follows:

- To evaluate the efficacy of prophylactic emicizumab in maintaining adequate control of bleeding
- To evaluate the clinical effect of prophylactic emicizumab on the number of joint bleeds over time
- To evaluate the clinical effect of prophylactic emicizumab on the number of target joint bleeds over time (target joints are defined as joints with  $\geq 3$  bleeds occurring in the same joint over the last 24 weeks prior to study entry)
- To evaluate the clinical effect of prophylactic emicizumab on the number of all bleeds (i.e., those treated and untreated with coagulation factors) over time
- To evaluate the clinical effect of prophylactic emicizumab on the number of spontaneous bleeds over time (spontaneous bleed rate)
- To evaluate the health-related quality of life (HRQoL) of patients according to Haem-A-QoL ( $\geq 18$ y) or Haemo-QoL\_SF (ages 12–17) scores after 24 weeks

- To evaluate the health status of patients according to EuroQoL 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) scores after 24 weeks
- To assess preference for emicizumab regimen compared with previous regimen used
- To assess the number of days away from school/work
- To assess the number of days hospitalized

### **Safety Objectives**

The safety objectives of this study are to evaluate the overall safety of emicizumab given Q4W in patients with hemophilia A based on the following endpoints:

- The incidence and severity of adverse events
- The incidence and severity of thromboembolic events
- Changes in physical examination findings and vital signs
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
- Incidence of thrombotic microangiopathy
- The incidence and clinical significance of anti-emicizumab antibodies
- The incidence of de novo development of FVIII inhibitors (non-inhibitor population)

### **Pharmacokinetic Objective**

The pharmacokinetic (PK) objective of this study is as follows:

- To characterize the pharmacokinetics of multiple Q4W SC doses of 6 mg/kg emicizumab

### **Exploratory Pharmacodynamic Biomarker Objective**

The exploratory PD biomarker objective is as follows:

- To investigate the effect of Q4W doses of emicizumab on PD parameters, including but not limited to aPTT, thrombin generation and FVIII activity at timepoints throughout the study

## **Study Design**

### **Description of Study**

Study BO39182 is a multicenter, open-label, non-randomized study designed to investigate the efficacy, pharmacokinetics, safety, and pharmacodynamics of emicizumab (6 mg/kg) administered in a Q4W dosing regimen. Patients with hemophilia A with or without inhibitors against FVIII will be enrolled. The study consists of two parts: a PK run-in part followed by an expansion part.

### **PK Run-In-Part**

In the PK run-in part, a full PK profile will be measured in the first 6 enrolled patients during the first 4 weeks to characterize the pharmacokinetics of a single SC dose of 6 mg/kg emicizumab in patients with hemophilia A. After the first and second emicizumab administration, an intense PK sampling will occur. A reduced PK sampling schedule will be used to characterize repeated Q4W SC administration from Week 9 to Week 21. After the sixth injection at Week 21, PK sampling frequency will be increased to characterize steady-state pharmacokinetics (see protocol).

An analysis of the data collected when all 6 patients in the PK run-in cohort have been followed for at least 6 weeks will be performed to assess whether the mean PK profile is as predicted (i.e.,  $\geq$  lower limit of 95% CI of the predicted mean PK profile) after repeated 6 mg/kg SC administration Q4W. In addition to PK, safety will be assessed in order to establish whether the expansion cohort can be opened. This analysis will be conducted by a Roche internal group of representatives from Clinical Pharmacology, Clinical Science, Clinical Safety, and Statistics; no formal Internal Monitoring Committee (IMC) will be set up.

### **Emicizumab—F. Hoffmann-La Roche Ltd**

21/Protocol BO39182, Version 3

## Expansion Part

An expansion phase will be conducted to further investigate the efficacy, pharmacokinetics, safety, and pharmacodynamics in a cohort of 40 patients. These patients will start with loading doses of 3 mg/kg QW  $\times$  4, followed by a maintenance dose of 6 mg/kg Q4W for at least 24 weeks overall. These patients will undergo PK sampling to investigate trough concentrations ( $C_{\text{trough}}$ ) and samples (predose) will be drawn as per the schedule of assessments (see protocol).

The primary analysis (descriptive analyses of the study objectives) will be conducted either after the last enrolled patient completes the 24-week treatment period, is lost to follow-up, or has withdrawn, whichever occurs first.

During the study, individual bleeds will be captured as they occur while HRQoL, health status, patients' preference and days of school or work missed will be assessed as outlined in the schedule of assessments in protocol. Patients (or their legally authorized representative) will be asked on a weekly basis to record via their electronic, handheld device whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a bleed has been given.

Physical examinations, vital signs, ECG, and laboratory assessments will be performed as detailed in the schedule of assessments (see protocol) and will be the same for all patients receiving emicizumab, regardless of whether they are enrolled in the PK run-in cohort or the expansion cohort. Adverse events will be captured on an ongoing basis, as they occur during the study.

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). There is clinical experience in the ongoing Phase I/II clinical studies with the treatment of over 60 breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents. FVIII, aPCC, or recombinant activated factor VII (rFVIIa) do not interfere with emicizumab PK assessments and no safety signals have been observed when breakthrough bleeds were treated with standard-of-care regimens during Phase I/II studies. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 3 events of TMA and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds. Therefore, it is recommended that breakthrough bleeds in the inhibitor population are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided. *In addition, caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients who are receiving emicizumab, and the use of anti-fibrinolytics is prohibited in conjunction with aPCC or Byclot®.*

Therefore, a washout period of 72 hours prior to the first emicizumab dose in this study is required for patients receiving prior aPCC or Byclot. Also a washout period of 72 hours for patients who were previously receiving ITI is required prior to the first emicizumab administration. Patients may require dosing with FVIII or for the treatment of potential breakthrough bleeds (see protocol), especially for the time period until steady-state concentrations of emicizumab have been reached.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation) will be collected as per the schedule of assessments and always coupled with a PK assessment for days where PK and PD samples are to be drawn. As values for many tests are normalized by even low plasma concentrations of emicizumab, a variety of assay formats (one-stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. It is not expected that these biomarkers will be used to guide the selection of patients to be treated with emicizumab. However, these biomarkers may be used to identify a future assay for the monitoring of emicizumab activity. In addition, factor IX (FIX) and factor X (FX) antigen levels will be monitored.

Biomarkers related to thromboembolism (e.g., D-dimer, prothrombin fragment 1.2) and immunologic biomarkers (i.e., anti-emicizumab antibodies and anti-FVIII antibodies) will be measured as per the schedule of assessments (see protocol).

Breakthrough bleeds will be treated with appropriate coagulation products with either FVIII (non-inhibitor patients) or rFVIIa (inhibitor patients) at the lowest expected dose to achieve hemostasis and captured as they occur. When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (day, start time), symptoms of bleed, and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use

of coagulation products (e.g., FVIII or rFVIIa) will be documented (e.g., bleeding, preventative dose before activity). Thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. For patients with inhibitors against FVIII who *receive* bypassing agents, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments.

All patients, irrespective of the cohort assigned, who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic emicizumab either within this study or as part of a future extension study according to Roche policy on post-study drug access. After 24 weeks on prophylactic emicizumab, all patients will be able to continue on their 6 mg/kg Q4W maintenance dose or may be provided the option to increase their dose to 3 mg/kg QW if they meet protocol-defined criteria of suboptimal response. Suboptimal response is defined as follows:

- $\geq 2$  qualifying bleeds within 24 weeks while on prophylactic emicizumab

Qualifying bleeds are defined as spontaneous, verified by investigator (e.g., by imaging or physical examination), and occurring while on prophylactic emicizumab at steady state (after the Week 5 visit for expansion cohort/after Week 17 visit for PK run-in cohort). These patients must receive approval from the Medical Monitor to increase their dose to 3 mg/kg QW.

Patients who discontinue emicizumab will be followed for 24 weeks after the last emicizumab dose.

### **Number of Patients**

Approximately 46 patients with congenital hemophilia A previously treated with either FVIII or bypassing agents will be enrolled in the study (6 patients in the PK run-in phase and 40 patients in the expansion phase).

### **Target Population**

#### Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (consent/assent will be taken as appropriate)
- Aged  $\geq 12$  years
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the patient-reported outcome (PRO) questionnaires and bleed diaries through the use of an electronic device
- Body weight  $\geq 40$  kg at screening
- Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors
- Patients using rFVIIa or willing to switch to rFVIIa as primary bypassing agent for the treatment of breakthrough bleeds
- FVIII inhibitor test during screening with titer results available prior to first administration of study drug
- Patients without FVIII inhibitors ( $<0.6$  BU/mL;  $<1.0$  BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL) who completed successful ITI must have done so at least 5 years before screening and must have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor  $>0.6$  BU/mL ( $>1.0$  BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL) since ITI
- For patients to be enrolled into PK run-in cohort:
  - Current episodic treatment (FVIII or bypassing agents) at the time of entry into this study and documentation of details of episodic treatment for at least 24 weeks prior to entry into this study



- For patients to be enrolled into the expansion cohort:  
Documentation of details of prophylactic or episodic treatment (FVIII or bypassing agents) and the number of bleeding episodes for at least 24 weeks prior to entry into this study  
For patients on an episodic regimen,  $\geq 5$  bleeds in the prior 24 weeks, regardless of inhibitor status
- Adequate hematologic function, defined as a platelet count  $\geq 100,000/\mu\text{L}$  and hemoglobin  $\geq 8$  g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin  $\leq 1.5 \times$  age-adapted upper limit of normal (ULN) (excluding Gilbert's syndrome) and both AST and ALT  $\leq 3 \times$  age-adapted ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine  $\leq 2.5 \times$  age-adapted ULN and creatinine clearance  $\geq 30$  mL/min by Cockcroft-Gault formula
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of  $< 1\%$  per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug  
A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ( $\geq 1$  year of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)  
Examples of highly effective contraceptive methods with a failure rate of  $< 1\%$  per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of  $< 1\%$  per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide  
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods for contraception.

#### Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing or planned ITI therapy; patients in whom ITI has failed will be eligible with a 72-hour washout period prior to the first emicizumab administration.
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment
- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study

- Known HIV infection with CD4 counts <200 cells/ $\mu$ L  
HIV infection with CD4 counts  $\geq$ 200 cell/ $\mu$ L permitted
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Concomitant disease, condition, significant abnormality on screening evaluations or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator/co-investigator, pose an additional unacceptable risk in administering study drug to the patient
- Receipt of any of the following:
  - Emicizumab in a prior investigational study
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
  - A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
  - Any other investigational drug currently being administered or planned to be administered
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnancy or lactation or intention to become pregnant during the study
- Women with a positive serum pregnancy test result within 7 days prior to initiation of study drug

### **End of Study**

The end of this study is defined as the date when the last remaining patient has completed the last visit (last patient last visit [LPLV]), as defined by any of the following criteria:

- Completion of at least 24 weeks of emicizumab treatment and either transfer to a separate extension study to receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products

OR

- Completion of the end-of-study safety follow-up visit 24 weeks after discontinuing emicizumab

OR

- Withdrawal of consent

OR

- Lost to follow-up

### **Length of Study**

The length of the study for an individual patient will be:

- Screening period up to 4 weeks
- Treatment and observation period at least 24 weeks
- *For patients who discontinue emicizumab treatment, safety follow-up visit 24 weeks after discontinuing emicizumab*

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 20 months.

### **Investigational Medicinal Products**

#### **Test Product (Investigational Drug)**

The emicizumab regimen being tested is 3 mg/kg QW for 4 weeks followed by 6 mg/kg Q4W subcutaneously for 24 weeks. All patients with suboptimal control may have the option to increase the dose to 3 mg/kg QW after 24 weeks, with approval from the Medical Monitor

## **Non-Investigational Medicinal Products**

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF page.

Concomitant use of the following drugs and therapies will be permitted:

- For patients in the expansion cohort who are on FVIII prophylaxis, they may continue their regular FVIII prophylaxis until the second emicizumab loading dose in order to avoid bleeds before adequate emicizumab level is reached. Concomitant routine FVIII prophylaxis is not otherwise permissible during the study.
- Drugs intended to control bleeds, including FVIII concentrates (non-inhibitor patients) or rFVIIa (inhibitor patients), should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve hemostasis may be lower than the FVIII or bypassing agent doses used prior to starting the study.

Caution should be taken for patients who are using rFVIIa (e.g., consideration of using no more than 90 µg/kg rFVIIa as an initial dose).

*Use of aPCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed with no more than 50 units/kg of aPCC to be administered as an initial dose. For patients receiving aPCC prior to study entry, a washout period of 72 hours prior to first emicizumab dosing is required.*

Other bypassing agents (e.g., Byclot) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 µg/kg of Byclot). For patients receiving Byclot prior to study entry, a washout period of 72 hours prior to first emicizumab dosing is required.

Exact dose and schedule of FVIII or bypassing agents should be discussed with patients at the beginning and throughout the study. Repeated dosing of FVIII, rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision and consideration should be given to verifying bleeds prior to repeated dosing. For rFVIIa, aPCC, and other bypassing agents, laboratory monitoring by additional local and central laboratory assessments should be performed as per the schedule of assessments.

- *Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab.*
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, and so on, that are not considered to result in systemic exposure
- Drugs to treat an existing medical condition ongoing at study entry that do not violate the eligibility criteria (e.g., anti-retroviral therapy for HIV infections)

## **Statistical Methods**

### **Primary Analysis**

The efficacy objective is to evaluate the clinical effect of 6 mg/kg emicizumab Q4W based on the number of bleeds over time.

The analyses will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of the time that each patient stays in the study included as an offset in the model.

The number of bleeds will be also annualized (Annualized Bleeding Rate—ABR) for each patient using the following formula:

$$ABR = \left( \frac{\text{Number of bleeds during the efficacy period}}{\text{Total number of days during the efficacy period}} \right) \times 365.25$$

In case the negative binomial model does not converge the above formula will be used as the sole method of analysis.

The clinical effect of prophylactic emicizumab on the number of bleeds, joint bleeds, target joint bleeds, spontaneous bleeds and all bleeds (i.e., those treated and untreated with coagulation factors) over time will be evaluated.

The number of bleeds, sites of bleeds, and types of bleeds will be summarized for all patients and listed for each patient individually. Several exploratory analyses will be conducted to characterize the type, location, duration, frequency, and pattern of bleeds. For continuous endpoints, descriptive statistics will be calculated and categorical endpoints will be characterized through frequency tables.

The primary final analysis will be performed 24 weeks after the last enrolled patient started treatment or has withdrawn prematurely, whichever occurs first.

### **Safety Analyses**

The safety analyses population will be based on all patients who received at least one administration of emicizumab. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts), ECGs, vital signs, anti-drug antibodies (ADAs), and de novo anti-FVIII inhibitors.

To evaluate the overall safety of emicizumab, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade.

For clinical laboratory data, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

### **Pharmacokinetic Analyses**

#### **PK Run-In Cohort**

PK parameters of emicizumab will be estimated using non-compartmental methods after the first and the sixth injections and include:

- $T_{max}$ : Time to maximum observed plasma concentration
- $C_{max}$ : Maximum observed plasma concentration
- $AUC_{\tau}$ : Area under the plasma concentration–time curve over a dosing interval
- $AUC_{0-inf}$ : Area under the plasma concentration–time curve between time zero (predose) extrapolated to infinity (only for the first injection)
- $t_{1/2}$ : Apparent terminal half-life
- $CL/F$  and  $CL_{ss}/F$ : Apparent Clearance

Concentration data and calculated PK parameters for emicizumab will be presented in individual listings, summary tables (including descriptive statistics: mean, geometric means, medians, ranges, standard deviations, and coefficients of variation) and graphs (including concentration versus time plots on linear and semi-logarithmic scales) as appropriate.

#### **Expansion Cohort**

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age,

gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies and completed Phase III studies. These analyses will be reported in a dedicated report.

### **Immunogenicity Analyses**

The immunogenicity analyses will include patients with at least one predose and one postdose ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e.,  $\geq 0.60$  titer units) than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

### **Exploratory Analyses**

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

### **Determination of Sample Size**

The sample size of 6 patients for the PK run-in cohort is considered appropriate to assess pharmacokinetics and safety to allow for an informed decision to open the subsequent expansion cohort with 40 additional patients.

The overall sample size of 40 patients in the expansion cohort is based primarily on clinical considerations taking into account the limited number of patients with hemophilia A.

### **Planned Interim Analysis**

An analysis of pharmacokinetics and safety will occur when the first 6 patients have been on treatment for 6 weeks. On the basis of the results for pharmacokinetics and safety (e.g.,  $\geq$  lower limit of 95% CI of the predicted mean PK profile, no severe unexpected safety findings), the study will proceed with the expansion cohort.

This analysis will be conducted by a Roche internal group of representatives from Clinical Pharmacology, Clinical Science, Clinical Safety and Statistics; no formal IMC will be set up.

## **LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

Abbreviation	Definition
ABR	annualized bleeding rate
ADA	anti-drug antibody
aHUS	atypical hemolytic uremic syndrome
aPCC	activated prothrombin complex concentrate
AUC	area under the concentration–time curve
AUC <sub>t</sub>	area under the concentration–time curve over a dosing interval
C <sub>avg,ss</sub>	average steady-state concentration
C <sub>max</sub>	maximum concentration observed
C <sub>trough</sub>	steady-state concentration at end of dosing interval
CVAD	central venous access device
cyFcγR	cynomolgus monkey Fcγ receptor
cyFcRn	cynomolgus monkey neonatal Fc receptor
EC	Ethics Committee
eCRF	electronic Case Report Form
EQ-5D-5L	European Quality of Life 5-Dimension, 5-Level questionnaire
EDC	electronic data capture
FDA	Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIX	factor IX
FIX:Ag	factor IX antigen
FIXa	activated factor IX
FVIII	factor VIII
FX	factor X
FX:Ag	factor X antigen
HCP	healthcare provider
hFcγR	human Fcγ receptor
hFcRn	human neonatal Fc receptor
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IND	Investigational New Drug (application)

Abbreviation	Definition
IRB	Institutional Review Board
ITI	immune tolerance induction
IV	intravenous
LPLV	last patient, last visit
MAD	multiple ascending dose
MN	mobile nursing
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QW	weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
RBR	Research Biosample Repository
rFVIII	recombinant factor VIII
rFVIIa	recombinant activated factor VII
SAD	single ascending dose
$t_{1/2}$	half-life
TMA	thrombotic microangiopathy
$t_{max}$	time to maximum plasma concentration
ULN	upper limit of normal
VAS	visual analog scale

## **1. BACKGROUND**

### **1.1 BACKGROUND ON HEMOPHILIA A**

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade ([Mannucci and Tuddenham 2001](#); [Franchini and Mannucci 2013](#)).

Hemophilia A is most commonly caused by an inherited FVIII gene mutation within the Xq28 region of the X chromosome. It occurs almost exclusively in men having one defective copy of the relevant gene on their X chromosome. Because an affected male will transmit a normal Y chromosome to all his sons and an abnormal X chromosome to all his daughters, his sons will not be affected and all of his daughters will be carriers. The offspring of a female carrier will have a 50% chance to receive a mutated FVIII gene; thus, hemophilia A will be transmitted to half the male infants and half of female infants will be carriers. Females who are carriers of hemophilia A may experience bleeding symptoms similar to those seen in men with mild hemophilia A, as approximately 10% of carriers have a FVIII activity less than 35% ([Plug and Mauser-Bunschoten 2006](#)). Rarely, women can have more severe bleeding symptoms requiring treatment and may develop FVIII inhibitors. Approximately 30% of patients with hemophilia A do not have a family history of the disorder; these cases arise from spontaneous FVIII gene mutations.

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity. Approximately 68% of people with hemophilia A have moderate (25%) or severe (43%) forms, characterized by FVIII activity levels < 5% or < 1%, respectively, leading to frequent bleeding events (bleeds) with the sequelae of musculoskeletal complications (e.g., arthropathy), local functional deficits, hemorrhagic shock, neurocognitive defects, or even death ([World Federation of Hemophilia 2013](#)).

#### **1.1.1 Management**

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimize bleeding events and complications ([Manco-Johnson et al. 2007](#)). Since the 1990s, recombinant FVIII (rFVIII) concentrates have been standard-of-care treatment options for patients with hemophilia A ([Kingdon and Lundblad 2002](#)). Treatment regimens to achieve optimal prevention of bleeding events vary individually; some patients tolerate trough FVIII levels of 1%, whereas, others require higher nadir FVIII levels to achieve the desired therapeutic outcome ([Ahnstrom et al. 2004](#); [Collins et al. 2010](#)). Current prophylactic regimens commonly use intravenous (IV) infusion therapy administered three times weekly; other regimens use every other day administration ([Shapiro 2013](#)).



Prophylactic FVIII replacement therapy has been recognized as superior to episodic treatment of symptomatic bleeds for several decades ([Khawaji et al. 2012](#)), and was adopted by national and international organizations as the desired treatment approach. However, the burden of treatment ([Eton et al. 2013](#); [Mair and May 2014](#)) is extraordinarily onerous, as adequate prophylaxis requires a lifetime of self-administered IV infusion of FVIII 3–4 times each week. In addition to the obvious toll on the quality of patients' quality of life ([Teal et al. 2014](#)), this burden results in suboptimal care for many who elect to avoid routine prophylaxis, despite its medical advantage ([Geraghty et al. 2006](#); [Lindvall et al. 2006](#), [De Moerloose et al. 2008](#); [Collins et al. 2014](#); [Oldenburg 2015](#)). Thus, episodic therapy is a standard-of-care for many patients with hemophilia in developed countries, where approximately one-third to one-half of the patients use FVIII on demand and avoid continuous prophylaxis. For example, a recent analysis reveals that in North America and Europe, only 44.3% of 1238 patients with severe hemophilia A are treated with routine FVIII prophylaxis ([Oldenburg and Brackmann 2014](#)). Similarly, prophylaxis was routinely offered to adults in only 18 of 35 European countries surveyed, and in 12 out of those 18 countries, 50% or fewer adults received FVIII prophylaxis ([O'Mahony et al. 2013](#)). In addition to treatment burden, other reasons including venous access and cost concerns underlie this problem ([Gringeri et al. 2012](#)), which contributes to hemophilia-associated long-term morbidity.

Although patients on FVIII prophylaxis experience a low number of bleeds, magnetic resonance imaging (MRI) scans demonstrated progressive arthropathy in up to two-thirds of patients who receive an adequate primary prophylaxis regimen. These changes begin within the first decade of life and involve clinically “bleed-free” joints ([Kraft et al. 2012](#), [Olivieri et al. 2012](#)). Accordingly, 40% of men in the third decade of life reported presence of a target joint, reduced mobility, or chronic pain ([Fischer et al. 2013](#), [Noone et al. 2013](#)). These findings indicate that FVIII prophylaxis delays, but does not completely prevent, long-term skeletal morbidity ([Oldenburg 2015](#)). This is in part due to the challenges of adherence and in part due to micro-bleeds associated with low FVIII trough levels ([Ljung and Gretenkort 2015](#)). Due to the short half-life of FVIII, current prophylaxis regimens aim at maintaining FVIII levels at a trough of  $\geq 1\%$ , which restore hemostasis for only part of the time ([Valentino et al. 2012](#)). A study of patients with varying severities of hemophilia suggests that protection from joint bleeds occurs only at continuous FVIII levels over 12% ([Den Uijl et al. 2011](#)), and achieving higher FVIII activity, though difficult to accomplish with current regimens, has been recognized as a goal for optimal care in a position paper from the World Federation of Hemophilia ([Skinner 2012](#)).

Routine IV FVIII therapy relies on venous cannulation skills of patients and their care providers ([Hacker et al. 2001](#)). In particular, this issue plagues the care of children with hemophilia, in whom central venous access devices (CVADs [i.e., port-a-caths]) have been used regularly to overcome technical difficulties. Although CVADs make

prophylaxis feasible in young children, they are associated with complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis (Ewenstein et al. 2004). A recent prospective study reported that 183 lines were implanted in 99 patients and that 41% of patients had at least one infectious episode. The median time to line removal was 483 days (IQR: 143–1071) (Rodriguez et al. 2015). A Finnish retrospective study similarly reported that 47% of 106 catheters implanted in 58 patients had to be removed because of a complication (Vepsäläinen et al. 2015). In addition, significant healthcare provider (HCP) efforts are required to manage optimal treatment solutions and to overcome identified issues (Schrijvers et al. 2013). Thus, both the disease and its treatment affect patients' HRQoL.

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%–30% of patients with severe hemophilia A and in 3%–13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titer ( $\geq 5$  BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are prothrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., “bypassing agents”). Bypassing products include factor eight inhibitor bypassing activity (FEIBA), an activated prothrombin complex concentrate (aPCC; FEIBA will be henceforth referred to as aPCC), and NovoSeven® (recombinant activated human FVIIa [rFVIIa]; NovoSeven® will be henceforth referred to as rFVIIa) (Srivastava et al. 2013). Both have been used as prophylaxis to prevent bleeding in patients with inhibitors against FVIII (“inhibitor patients”); however, the only available product for this indication in most countries is aPCC. Of note, treatment of patients with congenital hemophilia A of any severity with high-titer inhibitors is similar, and their endogenous severity, as defined based on FVIII activity at diagnosis (mild, moderate, or severe), is no longer prognostic of their clinical phenotype and risk of bleeding.

aPCC may be associated with side effects, such as thromboembolic events, hypersensitivity reactions, myocardial infarction, and disseminated intravascular coagulation. Both aPCC and rFVIIa are administered intravenously, with aPCC prophylaxis requiring every-other-day dosing and rFVIIa requiring daily (or more frequent) dosing.

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is important to reduce the time and burden associated with frequent IV dosing and the impact of the disease on aspects of physical health and other areas of function. A study assessing the relationship between self-reported adherence to prophylaxis and health outcomes (HRQoL and bleeding episodes) showed that poorer adherence with prophylaxis was associated with a greater number of self-reported bleeding episodes, more days of work/school missed among pediatric patients, and lower physical health status scores among pediatric patients (Krishnan et al. 2015). Adherence to prophylaxis by patients with hemophilia A,

defined as the extent to which a person's behavior corresponds to agreed recommendations by a healthcare provider (WHO 2003), ranges from 44% to 87% (Llewellyn et al. 2003; De Moerloose et al. 2008; Ho et al. 2013). In a Dutch study investigating patient behavior impacting adherence to prophylactic treatment, patients were asked about their experience with and adherence to administration of prophylaxis. Remarkably, some patients willingly chose non-adherence because they did not want to adapt their activities to hemophilia, and they were prepared to accept the consequences of their decision. Patients noted the difficulties of regular prophylaxis due to inadequate routine and the complexity of the needed self-management skills including planning, management of the treatment of bleeds, forgetfulness, stock management, and overruling activities in life (Schrijvers et al. 2015). There is a true need for therapeutics that have reliable efficacy, a long half-life, low treatment burden, and ease of administration to prevent bleeding in and minimize long-term morbidity of individuals with hemophilia A.

## **1.2 BACKGROUND ON EMICIZUMAB**

### **1.2.1 Molecule and Preclinical Data**

Emicizumab (also known as RO5534262 and ACE910) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of FVIII. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because the pharmacokinetic (PK) properties of this antibody are expected to enable marked extension of the dosing interval to once weekly, every 2 weeks, or every 4 weeks, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and low burden prophylactic therapy.

Binding studies of emicizumab to cynomolgus monkey factor IX (FIX) and FX showed a similar affinity as to the human factors. Mechanistic in vitro studies were conducted in human and cynomolgus FVIII-neutralized plasma and in various coagulation factor-specific assay-testing systems, which revealed that emicizumab shortened aPTT and promoted thrombin generation. Emicizumab bound to human Fcγ receptor (hFcγR), cynomolgus monkey Fcγ receptor (cyFcγR), human neonatal Fc receptor (hFcRn), and cynomolgus monkey neonatal Fc receptor (cyFcRn) with similar affinities as a humanized IgG4 reference antibody, natalizumab.

In vivo pharmacology experiments in cynomolgus monkeys were conducted in a hemophilia A model where endogenous FVIII levels were neutralized by a FVIII-specific monoclonal antibody. This model mimics essential characteristics of patients with hemophilia A and was used to test in vivo pharmacodynamics and efficacy under

spontaneous or local trauma-induced bleeding conditions. In summary, emicizumab demonstrated the ability to significantly reduce bleeding tendency under both sets of conditions.

Potential prothrombotic risks associated with emicizumab-induced FVIII mimetic activity were further explored in an in vivo cynomolgus monkey venous stasis model. In this model, thrombus formation in the presence of emicizumab was compared with that in the presence of FVIII or bypassing agents (rFVIIa or aPCC). Thrombus formation with emicizumab did not markedly exceed formation observed with rFVIIa, aPCC, or FVIII.

The pharmacokinetics/toxicokinetics of emicizumab were assessed in cynomolgus monkeys after single and multiple doses were administered intravenously and via the intended clinical SC route. After a single IV dose of 6 mg/kg emicizumab in male cynomolgus monkeys, the plasma clearance was 3.62 mL/day/kg and the terminal plasma half-life ( $t_{1/2}$ ) of emicizumab was 19.4 days. The single SC administration study (dose levels: 0.06, 0.6, and 6 mg/kg) indicated slow (time to maximum plasma concentration [ $t_{max}$ ]: 3.00–5.33 days) and complete absorption (bioavailability: 102% at 6 mg/kg). The IV and SC multiple dosing studies (toxicokinetic monitoring) revealed a  $t_{1/2}$  in the range of 14.9–30.8 days. Overall, exposures in terms of maximum plasma concentration ( $C_{max}$ ) and area under the concentration–time curve (AUC) increased in an approximately dose proportional manner.

A subfraction of the cynomolgus monkeys treated with repeated doses of emicizumab showed the formation of anti-emicizumab antibodies (which is expected with humanized monoclonal antibodies) with few animals also showing neutralizing antibodies.

Aspects of acute as well as repeated-dose toxicity including local tolerance assessment were evaluated in cynomolgus monkeys in 4-, 13-, and 26-week SC dose toxicity studies (at doses up to 30 mg/kg weekly) and a 4-week IV dose toxicity study (at doses up to 100 mg/kg weekly). No toxicologically relevant changes attributable to SC or IV administration of emicizumab were observed; the no observed adverse effect level (NOAEL) was the highest tested dose in each toxicity study.

See the RO5543262 (Emicizumab) Investigator's Brochure for additional details on nonclinical studies with emicizumab.

### **1.2.2      Clinical Experience**

Currently available experience with emicizumab in humans includes data from one completed Phase I study (ACE001JP—Last Patient Last Visit on 17 April 2015) and its ongoing extension, a Phase I/II study (ACE002JP). ACE001JP was a single study conducted in 3 parts, including both healthy subjects (Part A and Part B) and patients with hemophilia A (Part C). The objective of Parts A and B in healthy subjects was to investigate the tolerability, safety, PK, and pharmacodynamic (PD) response of SC-administered emicizumab in adult Japanese and Caucasian men and to evaluate for

racial differences, if any, in their PK and PD response. Healthy male volunteers aged 20–44 were eligible for enrollment. A total of 64 healthy volunteers were enrolled in Parts A and B from August 2012 to April 2013. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC administered emicizumab in patients with hemophilia A. Patients were eligible for enrollment if they were 12–59 years of age,  $\geq 40$  kg in weight, had a diagnosis of severe congenital hemophilia A, and had documentation of bleeds and/or treatment with coagulation factor in the last 6 months. For those with inhibitors, patients must have had  $\geq 6$  bleeds in the 6 months prior to enrollment, and for those without inhibitors, patients were required to have received  $\geq 150$  lifetime doses of FVIII replacement, including in the last 6 months. A total of 18 patients with hemophilia A were enrolled from May 2013 to June 2014.

Parts A and B of Study ACE001JP (completed) consisted of a randomized, placebo-controlled, single ascending dose (SAD) study, which was conducted in Japanese ( $n=40$ ; Part A) and Caucasian ( $n=24$ ; Part B) healthy men; 48 subjects received a single SC injection of 0.001 mg/kg to 1 mg/kg of emicizumab and 16 subjects received a single SC injection of placebo. Part C of Study ACE001JP was an open-label, multiple ascending dose (MAD) study in 18 Japanese patients with hemophilia A, both with and without inhibitors. Of note, patients received concurrent coagulation factor products to control breakthrough bleeds. Of the 18 patients in Part C of Study ACE001JP, 6 patients were dosed with 0.3 mg/kg/week SC following a single loading dose of 1 mg/kg SC, 6 patients were dosed with 1 mg/kg/week SC following a single loading dose of 3 mg/kg, and 6 patients received 3 mg/kg/week of emicizumab without a loading dose.

Study ACE002JP is an extension study that allows patients enrolled in Part C of Study ACE001JP to continue treatment with emicizumab. In order to be eligible for the extension study, patients must have completed 12 weeks of assigned treatment in Study ACE001JP and had bleeds prior to study entry. Seventeen of 18 patients in Part C of Study ACE001JP completed the 12-week treatment period. One patient discontinued the treatment and moved to the post-discontinuation follow-up period. A total of 16 of the 17 patients who completed the 12-week treatment period subsequently enrolled into extension Study ACE002JP, and 1 of the 17 patients moved to the post-treatment observation period of Study ACE001JP. Thus, the ongoing extension study, ACE002JP, includes 6 patients from the 0.3 mg/kg/week group, 5 patients from the 1 mg/kg/week group, and 5 patients from the 3 mg/kg/week group of Study ACE001JP. The investigator discontinued emicizumab for 1 adolescent patient with mild local injection-site reactions and a pre-study history of allergic reactions. Another patient, who had a pre-enrollment annualized bleeding rate (ABR) 0 on FVIII prophylaxis, was not allowed to enroll in the extension study due to a health authority requirement for a history of bleeds pre-enrollment. As Study ACE002JP allows for dose escalation in patients with a suboptimal response but no significant toxicity on their

current emicizumab dose, 2 of 6 patients eventually had their dose escalated from 0.3 mg/kg/week to 1 mg/kg/week and then to 3 mg/kg/week.

Data from the completed Parts A, B, and C of Study ACE001JP and interim data from Study ACE002JP (as of the cutoff date of 17 April 2015) are presented here; for further updated information, consult the current RO5534262 (Emicizumab) Investigator's Brochure. All continuing patients in Study ACE002JP have been observed for at least 96, 72, or 48 weeks in the 0.3, 1, and 3 mg/kg/week dosing groups, respectively, except for 1 patient in the 3 mg/kg/week group who has only been followed for 44 weeks.

The median age and body mass index (BMI) of the healthy volunteers across the dose groups in Part A ranged from 25.5–35.5 years and 20.28–21.44 kg/m<sup>2</sup>, respectively. In Part B, the median age ranged from 28.5–30.5 years, and the median BMI ranged from 21.60–22.56 kg/m<sup>2</sup> across the dose groups. Among the 0.3, 1, and 3 mg/kg/week groups in Part C, the median age was 32, 30, and 33 years, respectively; the median BMI was 22.54, 22.87, and 22.31 kg/m<sup>2</sup>, respectively. There were 5 adolescent patients (12–18 years): 1 patient (■■ years old) in the 0.3 mg/kg/week group; 2 patients (■■ years old and ■■ years old) in the 1 mg/kg/week group; and 2 patients (■■ years old and ■■ years old) in the 3 mg/kg/week group. There were 11 patients with inhibitors: 4 patients in the 0.3 mg/kg/week group; 4 patients in the 1 mg/kg/week group; and 3 patients in the 3 mg/kg/week group. All patients in Part C of Study ACE001JP have completed the treatment period and have either subsequently enrolled in the extension Study ACE002JP (16 of 18 patients) or moved to the follow-up or observation period (2 of 18 patients).

In the 0.3 mg/kg/week cohort, 1 patient transitioned to the observation period of the ACE001JP study after 12 weeks of treatment and restarted the study treatment in the ACE002JP study at the increased dose of 1 mg/kg/week, approximately 35 weeks later. Another patient in the 0.3 mg/kg/week cohort had his dose increased in Study ACE002JP after completing 12 weeks of treatment in Study ACE001JP. Both of these patients eventually had their dose further increased to 3 mg/kg/week. A third patient in this group started to receive 1 mg/kg/week just prior to the data cutoff. At the data cutoff date of 17 April 2015, 6 patients in the 0.3 mg/kg/week group, 5 patients in the 1 mg/kg/week group, and 5 patients in 3 mg/kg/week group have continued emicizumab treatment in Study ACE002JP.

The efficacy parameter of ABR was calculated by annualizing the number of bleeds that required treatment with coagulation factor products during the 6 months prior to study enrollment and during the treatment period after first emicizumab administration. During the 6 months before study enrollment, the patients without inhibitors had received FVIII prophylactic replacement therapy, while the patients with inhibitors had received episodic therapy and/or prophylactic therapy with bypassing agents.

During the course of emicizumab administration, the ABR decreased in all patients compared with the ABR prior to study enrollment, regardless of whether or not they had inhibitors, with the exception of 1 patient without inhibitors in the 3 mg/kg/week group. This patient, who was previously on FVIII prophylaxis, had a baseline ABR of 0 and maintained an ABR of 0 during treatment with emicizumab. In the 0.3 mg/kg/week group, the ABR reduction ranged from 22.8%–100% in all patients. In the 1 mg/kg/week group, the ABR reduction ranged from 78.9%–100% in all patients (excluding the patients who were dose escalated from the 0.3 mg/kg/week group). In the 3 mg/kg/week group, the ABR reduction ranged from 86.4%–100% in all patients (excluding the patient with the baseline ABR of 0 and patients who were dose escalated from the 1 mg/kg/week group).

Emicizumab was safe and well tolerated in patients (see the Investigator's Brochure) in the Phase I/II studies. The majority of adverse events were of mild intensity, except for 5 moderate adverse events (upper respiratory tract infection, bipolar I disorder, hemophilia [i.e., left hip joint bleeding due to hemophilia], headache, and asthma) and 2 severe adverse events (appendicitis and mesenteric hematoma). Both severe events were considered to be serious adverse events and not related to emicizumab administration. A total of 7 patients reported injection-site reactions (including erythema, hematoma, rash, pain, discomfort and pruritus). All injection-site reactions were of mild intensity. Besides injection-site reactions, the most frequently reported adverse events ( $\geq 4$  patients) were nasopharyngitis, pharyngitis, dental caries, excoriation, and headache. There were no dose dependent increases in adverse events, and the majority of the adverse events were not considered related to emicizumab. Treatment was discontinued for 1 patient with injection-site erythema in the 1 mg/kg weekly group; the event was mild in intensity and resolved. This same patient also reported one non-related serious adverse event (hemophilia [i.e., left hip joint bleeding due to hemophilia]) approximately 24 weeks after the last dose of study drug. In the Phase I/II studies, no thromboembolic adverse events have been reported when emicizumab has been administered alone or concomitantly with FVIII products or bypassing agents as episodic therapy.

As of *April* 2017, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), thrombotic microangiopathy (TMA) was observed in 3 patients receiving emicizumab and bypassing agents; and 2 cases of thromboembolic events were observed in 2 patients receiving emicizumab and bypassing agents. For more details, refer to Sections [5.1.2.3](#) and [5.1.2.4](#).

Emicizumab exhibited linear PK after single SC administration. Following single SC injection, its mean elimination  $t_{1/2}$  (4–5 weeks) was similar to that of other human IgG antibodies. Furthermore, comparison of PK profiles between Japanese and Caucasian healthy volunteers did not reveal racial differences. In patients with hemophilia A, emicizumab trough plasma concentrations increased in a dose-proportional manner with weekly dosing to achieve a plateau after approximately 12 weeks in the first two dosing



groups, in which a loading dose was administered, and after approximately 24 weeks in the highest dose group, in which no initial loading dose was administered.

Until the cutoff in April 2015 emicizumab has been administered to 48 healthy subjects and 18 patients with hemophilia A. A total of 6 subjects/patients tested positive for anti-drug antibodies (ADAs) on at least one occasion. The presence or absence of ADAs had no impact on efficacy profiles in patients with hemophilia A. For further updated information, consult the current RO5534262 (Emicizumab) Investigator's Brochure.

### 1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study is designed to evaluate the efficacy, safety, pharmacokinetics, pharmacodynamics, HRQoL, and patient preference of emicizumab given every 4 weeks (Q4W) SC in patients with hemophilia A irrespective of FVIII inhibitor status, supported by the mode of action of emicizumab and the observation from Phase I/II studies of similar pharmacokinetics, efficacy, and safety between the inhibitor and non-inhibitor populations.

In the Phase I/II study (ACE001JP) 18 Japanese patients with hemophilia A, either with or without inhibitors, were treated with emicizumab at three different dosing regimens (0.3 mg/kg/week, 1 mg/kg/week, and 3 mg/kg/week). During the course of emicizumab administration, the ABR significantly decreased in all patients compared with the ABR prior to study enrollment, regardless of inhibitor status, with the exception of 1 patient without inhibitors in the 3 mg/kg/week group (see Section 1.2.2).

The dosing regimen investigated in this study (3 mg/kg weekly [QW]  $\times$  4 followed by 6 mg/kg Q4W) is being investigated to provide an option for patients to receive emicizumab every 4 weeks, while still delivering the same cumulative dose as the 1.5 mg/kg QW or 3 mg/kg every 2 weeks (Q2W) regimens currently being investigated in other Phase III studies. The Q4W regimen of 6 mg/kg is expected to result in a similar exposure (average steady-state concentration [ $C_{avg,ss}$ ]) as the 1.5 mg/kg QW and 3 mg/kg Q2W regimens despite higher  $C_{max}$  and lower  $C_{trough}$  levels at steady state (see Section 3.3).

Emicizumab was well tolerated in the Phase I/II studies. The majority of adverse events were of mild intensity, with the most common being injection-site reactions. The majority of the adverse events were not considered related to emicizumab. In these studies, no thromboembolic or systemic hypersensitivity adverse events were observed; however, in the ongoing Phase III Study BH29884, 3 cases of TMA and 2 thromboembolic events were observed in patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds. Three out of these 5 patients have fully recovered, *while 1 patient's condition has improved and 1 patient has died due to severe rectal bleeding* (see Sections 5.1.2.3 and Section 5.1.2.4).



The safety is additionally supported by a NOAEL of  $\geq 30$  mg/kg/week in cynomolgus monkeys. The data from this preclinical study estimate the maximum dose of 3 mg/kg QW used in the Phase I/II study was associated with a 10.3-fold and 11.2-fold safety margin based on  $C_{\max}$  and  $AUC_{\tau}$ , respectively, while the dose of 6 mg/kg Q4W investigated in the present study is predicted to be associated with corresponding 17.4- and 22.5-fold safety margins.

## **2. OBJECTIVES AND ENDPOINTS**

### **2.1 PHARMACOKINETIC RUN-IN PHASE**

#### **2.1.1 Objectives**

The objectives of the PK run-in are as follows:

- To investigate the pharmacokinetics of emicizumab after single and multiple (Q4W) SC administration of 6 mg/kg
- To assess the safety and tolerability of emicizumab after Q4W SC administration of 6 mg/kg
- To explore the prophylactic effect of emicizumab in maintaining adequate control of bleeding
- To investigate the effect of emicizumab on PD markers including (but not limited to) aPTT, thrombin generation, and FVIII activity

### **2.2 EXPANSION PHASE**

#### **2.2.1 Efficacy Objectives**

The efficacy objectives are as follows:

- To evaluate the efficacy of prophylactic emicizumab in maintaining adequate control of bleeding
- To evaluate the clinical effect of prophylactic emicizumab on the number of joint bleeds over time
- To evaluate the clinical effect of prophylactic emicizumab on the number of target joint bleeds over time (target joints are defined as joints with  $\geq 3$  bleeds occurring in the same joint over the last 24 weeks prior to study entry)
- To evaluate the clinical effect of prophylactic emicizumab on the number of all bleeds (i.e., those treated and untreated with coagulation factors) over time
- To evaluate the clinical effect of prophylactic emicizumab on the number of spontaneous bleeds over time (spontaneous bleed rate)
- To evaluate the HRQoL of patients according to Haem-A-QoL ( $\geq 18$ y) or Haemo-QoL\_SF (ages 12–17) scores after 24 weeks
- To evaluate the health status of patients according to EuroQoL 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) scores after 24 weeks
- To assess preference for emicizumab regimen compared with previous regimen used

- To assess the number of days away from school/work
- To assess the number of days hospitalized

### **2.2.2      Safety Objectives**

The safety objectives of this study are to evaluate the overall safety of emicizumab given Q4W in patients with hemophilia A based on the following endpoints:

- The incidence and severity of adverse events
- The incidence and severity of thromboembolic events
- Changes in physical examination findings and vital signs
- Incidence of laboratory abnormalities
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to drug discontinuation
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
- Incidence of thrombotic microangiopathy
- The incidence and clinical significance of anti-emicizumab antibodies
- The incidence of de novo development of FVIII inhibitors (non-inhibitor population)

### **2.2.3      Pharmacokinetic Objective**

The PK objective of this study is as follows:

- To characterize the pharmacokinetics of multiple Q4W SC doses of 6 mg/kg emicizumab

### **2.2.4      Exploratory Pharmacodynamic Biomarker Objective**

The exploratory PD biomarker objective is as follows:

- To investigate the effect of Q4W doses of emicizumab on PD parameters, including but not limited to aPTT, thrombin generation and FVIII activity at timepoints throughout the study

## **3.              STUDY DESIGN**

### **3.1              DESCRIPTION OF THE STUDY**

Study BO39182 is a multicenter, open-label, non-randomized study designed to investigate the efficacy, pharmacokinetics, safety, and pharmacodynamics of emicizumab (6 mg/kg) administered in a Q4W dosing regimen. Patients with hemophilia A with or without inhibitors against FVIII will be enrolled. The study consists of two parts: a PK run-in part followed by an expansion part.

#### **3.1.1          PK Run-In Part**

In the PK run-in part, a full PK profile will be measured in the first 6 enrolled patients during the first 4 weeks to characterize the pharmacokinetics of a single SC dose of 6 mg/kg emicizumab in patients with hemophilia A. After the first and second

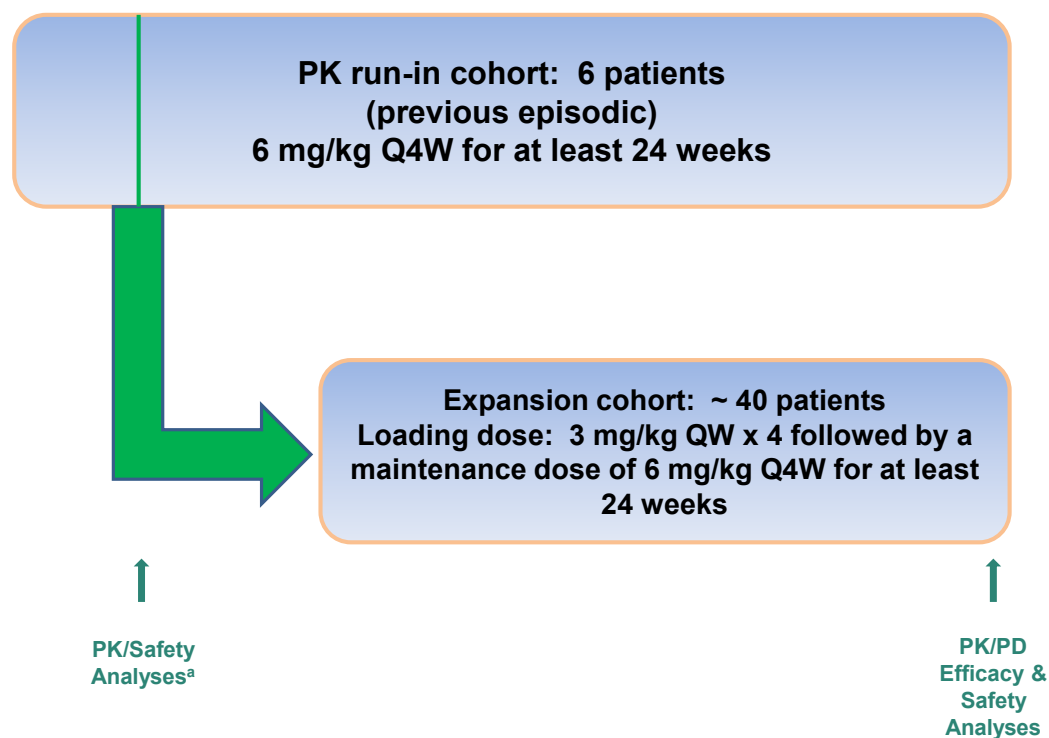
emicizumab administration, an intense PK sampling will occur. A reduced PK sampling schedule will be used to characterize repeated Q4W SC administration from Week 9 to Week 21. After the sixth injection at Week 21, PK sampling frequency will be increased to characterize steady-state pharmacokinetics (see [Appendix 2](#)).

An analysis of the data collected when all 6 patients in the PK run-in cohort have been followed for at least 6 weeks will be performed to assess whether the mean PK profile is as predicted (i.e.,  $\geq$  lower limit of 95% CI of the predicted mean PK profile) after repeated 6 mg/kg SC administration Q4W. In addition to PK, safety will be assessed in order to establish whether the expansion cohort can be opened. This analysis will be conducted by a Roche internal group of representatives from Clinical Pharmacology, Clinical Science, Clinical Safety, and Statistics; no formal Internal Monitoring Committee (IMC) will be set up.

### **3.1.2            Expansion Part**

An expansion phase will be conducted to further investigate the efficacy, pharmacokinetics, safety, and pharmacodynamics in a cohort of 40 patients. These patients will start with loading doses of 3 mg/kg QW  $\times$  4, followed by a maintenance dose of 6 mg/kg Q4W for at least 24 weeks overall. These patients will undergo PK sampling to investigate trough concentrations ( $C_{trough}$ ) and samples (predose) will be drawn as per the schedule of assessments (see [Appendix 2](#)).

**Figure 1 Study Schema**



PD= pharmacodynamic; PK= pharmacokinetic; Q4W= every 4 weeks.

<sup>a</sup> Analysis will occur when last patient enrolled in the PK run-in cohort has been in the study for 6 weeks.

The primary analysis (descriptive analyses of the study objectives) will be conducted either after the last enrolled patient completes the 24-week treatment period, is lost to follow-up, or has withdrawn, whichever occurs first.

During the study, individual bleeds will be captured as they occur while HRQoL, health status, patients' preference and days of school or work missed will be assessed as outlined in the schedule of assessments in protocol. Patients (or their legally authorized representative) will be asked on a weekly basis to record via their electronic, handheld device whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a bleed has been given.

Physical examinations, vital signs, ECG, and laboratory assessments will be performed as detailed in the schedule of assessments (see [Appendix 1](#)) and will be the same for all patients receiving emicizumab, regardless of whether they are enrolled in the PK run-in cohort or the expansion cohort. Adverse events will be captured on an ongoing basis, as they occur during the study.

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). There is clinical experience in the ongoing Phase I/II clinical studies with the treatment of over 60 breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents. FVIII, aPCC, or rFVIIa do not interfere with emicizumab PK assessments and no safety signals have been observed when breakthrough bleeds were treated with standard-of-care regimens during Phase I/II studies. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 3 events of TMA and 2 thromboembolic events were observed in patients who concomitantly used repeated doses of aPCC for the treatment of breakthrough bleeds (see Sections 5.1.2.3 and 5.1.2.4). Therefore, it is recommended that breakthrough bleeds in the inhibitor population are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided (see Section 4.4.1). *In addition, caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients who are receiving emicizumab, and the use of anti-fibrinolytics is prohibited in conjunction with aPCC or Byclot<sup>®</sup> (see Sections 4.4.1 and 4.4.2).*

Therefore, a washout period of 72 hours prior to the first emicizumab dose in this study is required for patients receiving prior aPCC or Byclot. Also a washout period of 72 hours for patients who were previously receiving ITI is required prior to the first emicizumab administration. Patients may require dosing with FVIII or for the treatment of potential breakthrough bleeds (see Section 4.4.1), especially for the time period until steady-state concentrations of emicizumab have been reached.

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation) will be collected as per the schedule of assessments and always coupled with a PK assessment for days where PK and PD samples are to be drawn (see Appendix 2). As values for many tests are normalized by even low plasma concentrations of emicizumab, a variety of assay formats (one-stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. It is not expected that these biomarkers will be used to guide the selection of patients to be treated with emicizumab. However, these biomarkers may be used to identify a future assay for the monitoring of emicizumab activity. In addition, FIX and FX antigen levels will be monitored.

Biomarkers related to thromboembolism (e.g., D-dimer, prothrombin fragment 1.2) and immunologic biomarkers (i.e., anti-emicizumab antibodies and anti-FVIII antibodies) will be measured as per the schedule of assessments (see Appendix 1).

Breakthrough bleeds will be treated with appropriate coagulation products with either FVIII (non-inhibitor patients) or rFVIIa (inhibitor patients) at the lowest expected dose to achieve hemostasis and captured as they occur (see Section 4.4.1). When a bleed has occurred, patients (or their legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed

(day, start time), symptoms of bleed, and treatment for bleed (e.g., other than emicizumab in case of breakthrough bleeds). The reason for the use of coagulation products (e.g., FVIII or rFVIIa) will be documented (e.g., bleeding, preventative dose before activity). Thorough documentation of the treatments for bleeds will be requested, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. For patients with inhibitors against FVIII who *receive* bypassing agents, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see [Appendix 1](#) and [Appendix 2](#)).

All patients, irrespective of the cohort assigned, who continue to derive clinical benefit will be given the opportunity to continue receiving prophylactic emicizumab either within this study or as part of a future extension study according to Roche policy on post-study drug access (see Section 4.3.4). After 24 weeks on prophylactic emicizumab, all patients will be able to continue on their 6 mg/kg Q4W maintenance dose or may be provided the option to increase their dose to 3 mg/kg QW if they meet protocol-defined criteria of suboptimal response. Suboptimal response is defined as follows:

- $\geq 2$  qualifying bleeds within 24 weeks while on prophylactic emicizumab

Qualifying bleeds are defined as spontaneous, verified by investigator (e.g., by imaging or physical examination), and occurring while on prophylactic emicizumab at steady state (after the Week 5 visit for expansion cohort/after Week 17 visit for PK run-in cohort). These patients must receive approval from the Medical Monitor to increase their dose to 3 mg/kg QW (see Section 4.3.2).

Patients who discontinue emicizumab will be followed for 24 weeks after the last emicizumab dose.

### **3.2 END OF STUDY AND LENGTH OF STUDY**

The end of this study is defined as the date when the last remaining patient has completed the last visit (last patient last visit [LPLV]), as defined by any of the following criteria:

- Completion of at least 24 weeks of emicizumab treatment and either transfer to a separate extension study to receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products

OR

- Completion of the end-of-study safety follow-up visit 24 weeks after discontinuing emicizumab

OR

- Withdrawal of consent

OR

- Lost to follow-up

The length of the study for an individual patient will be:

- Screening period up to 4 weeks
- Treatment and observation period at least 24 weeks
- *For patients who discontinue emicizumab treatment, safety follow-up visit 24 weeks after discontinuing emicizumab*

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 20 months.

### **3.3 RATIONALE FOR STUDY DESIGN**

The Sponsor proposes a multicenter, non-randomized Phase III clinical study that will enroll patients aged 12 years or older with severe hemophilia A, irrespective of inhibitor status. The study consists of a PK run-in cohort and an expansion cohort (see [Figure 1](#)) and will investigate a Q4W dosing regimen that would provide patients with a treatment option that requires less frequent dosing while providing a similar exposure compared with the emicizumab 1.5 mg/kg QW and emicizumab 3 mg/kg Q2W regimens that are currently under investigation.

The PK run-in cohort of 6 patients will provide substantial knowledge on pharmacokinetics (e.g., dose linearity and SC absorption) and will inform about preliminary safety and efficacy. As the patients will not receive a loading dose in this cohort and bleeds might not be optimally controlled by emicizumab at the study start, this cohort is restricted to patients previously receiving episodic treatment with either FVIII or bypassing agents.

The expansion cohort of 40 patients will investigate pharmacokinetics, safety, and efficacy in patients receiving a loading dose of 3 mg/kg QW  $\times$  4 followed by a maintenance dose of 6 mg/kg Q4W. This cohort will be open for patients who are on either episodic or prophylactic treatment prior to study.

The Q4W regimen option is investigated in this study in order to help address current challenges concerning the limited adherence to prophylaxis of 44%–87% in patients with hemophilia A ([Llewellyn et al. 2003](#); [De Moerloose et al. 2008](#); [Ho et al. 2013](#)). As major factors for limited adherence to prophylaxis are inadequate routine and the complexity of the needed self-management skills including planning, forgetfulness, and stock management ([Schrijvers et al. 2015](#)), a SC Q4W dosing regimen might address these challenges and reduce the treatment burden for patients with hemophilia A assigned to prophylaxis treatment (see Section [1.1](#)).

#### **3.3.1 Rationale for Emicizumab Dose and Schedule**

Phase III dosing regimens have been proposed based on modeling and simulation of the PK and efficacy data from patients participating in Part C of Study ACE001JP and in Study ACE002JP.

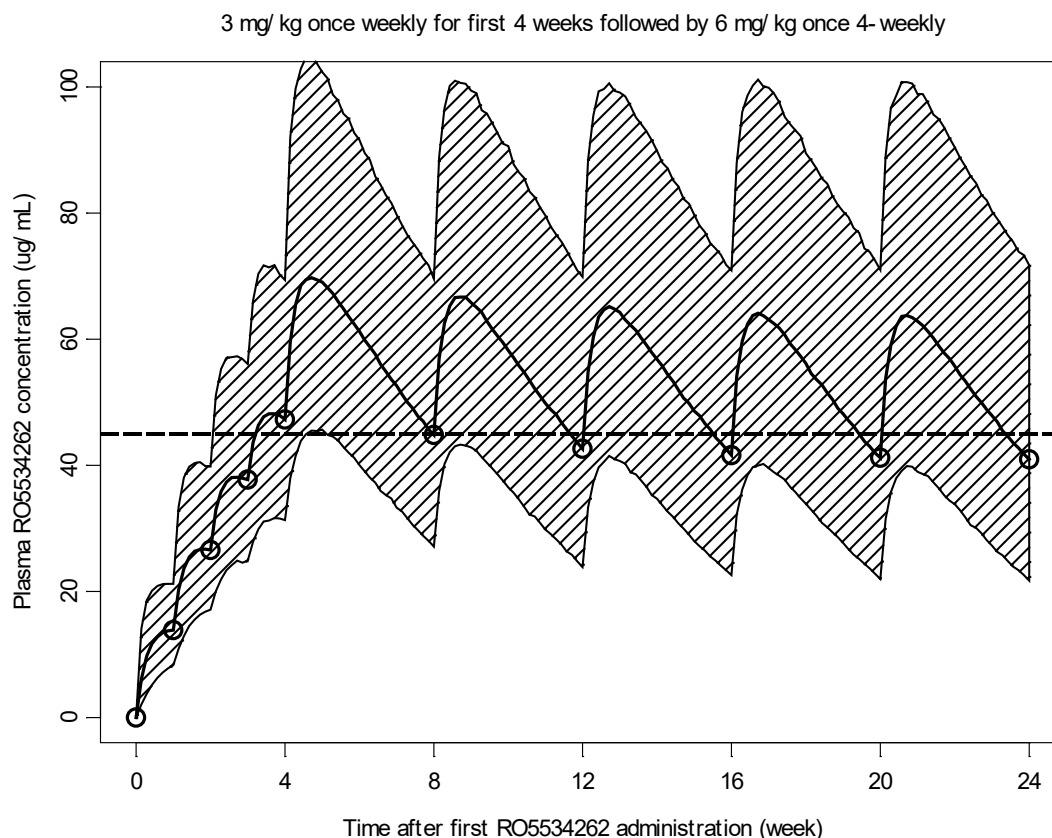
Single- and multiple-dose pharmacokinetics of emicizumab were characterized in Phase I and Phase II studies at doses up to 1 mg/kg and 3 mg/kg, respectively. After a single dose, the emicizumab plasma concentrations peaked 1–2 weeks after dosing. Plasma concentrations subsequently decreased with a mean elimination half-life ( $t_{1/2}$ ) of 28.3–34.4 days, without clear differences among doses. Emicizumab exhibited linear PK, with exposure increasing in proportion to the dose. After multiple doses, in patients with hemophilia A, emicizumab trough plasma concentrations increased in a dose-proportional manner with weekly dosing to achieve a plateau after approximately 12 weeks in groups in which a single loading dose was administered and after approximately 24 weeks in the highest dose group, in which no initial loading dose was administered.

The exposure/response relationship of emicizumab (predicted plasma concentration at the time of bleeding event/bleeding event) was previously characterized with repeated time-to-event (RTTE) modeling. Simulations suggested that a median ABR of 1 is achieved for emicizumab trough plasma concentrations  $\geq 16 \mu\text{g/mL}$  and a median ABR of 0 for emicizumab trough plasma concentrations  $\geq 45 \mu\text{g/mL}$ . To achieve this level, once-weekly loading doses of 3 mg/kg for the first 4 weeks followed by QW maintenance doses of 1.5 mg/kg or Q2W maintenance doses of 3 mg/kg have been recommended for the other Phase III studies.

A dose of 6 mg/kg Q4W is equivalent in terms of cumulative dose to the dose levels of 1.5 mg QW or 3 mg/kg Q2W that are being evaluated in the other Phase III studies. Assuming linear PK up to 6 mg/kg, model-based simulations were used to explore whether a Q4W dosing regimen could provide sufficient efficacy. Simulations showed that a once-weekly loading dose of 3 mg/kg for the first 4 weeks, followed by an every 4-week maintenance dose of 6 mg/kg would provide a steady-state  $C_{\text{max}}$  and  $\text{AUC}_{\tau}$  of  $78.1 \pm 20.9 \mu\text{g/mL}$  and  $1570 \pm 447 \text{ day} \cdot \mu\text{g/mL}$ , respectively. While more than half of the patients would not be expected to have a trough level of  $\geq 45 \mu\text{g/mL}$  at steady state, the simulated ABR distribution was similar to the planned dosing regimens of other Phase III studies. This Q4W dosing regimen is, therefore, expected to maintain similar efficacy to the QW and Q2W dosing regimens.



**Figure 2 Simulated Plasma Emicizumab Concentration over Time (Q4W Dosing)**



Q4W=every 4 weeks.

Notes: Once-weekly loading dose of 3 mg/kg for first 4 weeks followed by every 4 weeks maintenance dose of 6 mg/kg was applied.

X-axis=time after first emicizumab administration (week).

Y-axis=plasma emicizumab concentration ( $\mu\text{g/mL}$ ).

Dots and solid line=simulated median plotted at each trough sampling timepoint.

Shaded area=simulated 5- to 95-percentile range.

Broken line=target exposure level of 45  $\mu\text{g/mL}$ .

Overall, a Q4W dosing regimen with 6 mg/kg is expected to provide favorable safety and efficacy in patients with hemophilia A with or without inhibitors.

### **3.3.2 Rationale for Patient Population**

This study will include patients with hemophilia A, irrespective of the presence of FVIII inhibitors. The mode of action of emicizumab is identical in the inhibitor and non-inhibitor populations, and data from Phase I/II studies did not show a difference in pharmacokinetics, safety, or efficacy between patients with or without inhibitors against FVIII. Ideally, a representative variety of patients with hemophilia A should be enrolled

in this Q4W study (e.g., to include 10–12 patients with inhibitors out of the total of approximately 46 patients) in order to investigate further PK in both inhibitor and non-inhibitor populations.

For the PK run-in part only, patients on an episodic treatment regimen at time of enrollment are allowed to enter because, in this cohort (who do not receive loading dose), the likelihood of breakthrough bleeds is higher based on the steady state concentrations of emicizumab, which are expected to be reached after only 24 weeks.

Although the severity of a patient's hemophilia A is directly related to the FVIII activity, inter-patient variability may exist based on level of physical activity, bleeding history, and other features. Therefore, patients previously treated with episodic FVIII or bypassing agents will be required to have at least 5 bleeds in the last 24 weeks prior to study entry to be eligible for enrollment into the expansion cohort. This requirement is intended to select a group of patients with hemophilia A who have a high, unmet medical need and to enable evaluation of adequate control of bleeding in this population. Patients who have been on previous prophylactic treatment can enroll (in the expansion phase only) without any requirement for a certain bleed number because these patients' bleeds should be well controlled through receiving their current standard of care. In order to exclude patients who might have a higher chance to show an immune response to foreign protein regimens (e.g., FVIII), patients without FVIII inhibitors ( $<0.6$  BU/mL;  *$<1.0$  BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of  $1.0$  BU/mL*) who completed successful immune tolerance induction (ITI) at least 5 years before screening must have no evidence of inhibitor recurrence (permanent or temporary), indicated by detection of an inhibitor, FVIII half-life  $<6$  hours, or FVIII recovery  $<66\%$  since ITI ([Antun et al. 2015](#)).

### **3.3.3 Rationale for Biomarker Assessments**

Biomarkers to measure the PD effect of emicizumab on hemostasis have not been fully validated to date and require further testing to determine which assays and technical conditions are most suitable for use with emicizumab treatment. Plasma samples will be collected for PD biomarker assessment in parallel with PK samples at all clinic visits to demonstrate evidence of biologic activity of emicizumab in patients and to support evaluation of the Q4W dosing regimen. These PD biomarkers include but are not limited to coagulation assays such as aPTT, thrombin generation, and FVIII activity assays. All of these assays were previously shown in the Phase I/II study to exhibit a dose-response relationship to emicizumab concentration (for more information, see the Investigator's Brochure). The aPTT assay will be run both in standard form and with a modification to ensure that the assay range covers all levels of emicizumab exposure. In addition, clot waveform analysis may be run as an exploratory PD coagulation assay. Exploratory plasma biomarkers will include factor IX antigen (FIX:Ag) and factor X antigen (FX:Ag) to assess whether drug treatment causes a change in the circulating levels of these coagulation factors, which are the binding targets of emicizumab, and may include

measurement of other coagulation or hemophilia-related factors as well. Finally, remaining plasma samples will be banked for future emicizumab-related research and will be stored for no longer than 5 years after study closure. No whole-blood samples will be collected except as used for local safety laboratory tests, and no DNA analysis will be performed in this study.

### **3.3.4 Rationale for Patient-Reported Outcome Assessments**

HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009). HRQoL in patients with hemophilia is multifaceted and impacted by disease symptoms (i.e., pain, bleeding), treatment (i.e., prophylactic and on-demand), anxiety (around infusions), and limitations in daily activities.

The goal of measuring HRQoL is to quantify the benefit of treatment from the patient perspective. Previous studies with adolescent patients treated with prophylactic regimens have reported improvements in physical health, feelings, view of self, family relations, friend relations, perceived support, relation with others, participation in sports, dealing with hemophilia, views of treatment, views of the future, and relationships (Santagostino et al. 2014). Improvements in physical health, feelings, view of self, and participation in work and school have also been observed in adults treated with prophylactic regimens (Stasyshyn et al. 2014).

The inclusion of HRQoL measures in the current study will allow for the longitudinal assessment of the impact of prophylactic treatment with emicizumab in adolescents and adults with hemophilia A and an evaluation of any changes from their baseline assessment.

The study will also include a measure designed to capture patient preference with treatment. Previous studies have noted that patients express preference for treatments that do not have negative effects (e.g., pain that results from infusions), are not time consuming, are not inconvenient, and have a goal of achieving a “normal life” (Cimino et al. 2014). The inclusion of a fit-for-purpose preference survey after treatment with emicizumab will provide information on whether SC is preferred to IV administration and explore potential underlying reasons.

## **4. MATERIALS AND METHODS**

### **4.1 PATIENTS**

Approximately 46 patients with congenital hemophilia A previously treated with either FVIII or bypassing agents will be enrolled in the study (6 patients in the PK run-in phase and 40 patients in the expansion phase).

#### **4.1.1 Inclusion Criteria**

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (consent/assent will be taken as appropriate)

- Aged  $\geq 12$  years
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the patient-reported outcome (PRO) questionnaires and bleed diaries through the use of an electronic device
- Body weight  $\geq 40$  kg at screening
- Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors
- Patients using rFVIIa or willing to switch to rFVIIa as primary bypassing agent for the treatment of breakthrough bleeds
- FVIII inhibitor test during screening with titer results available prior to first administration of study drug
- Patients without FVIII inhibitors ( $<0.6$  BU/mL;  *$< 1.0$  BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL*) who completed successful ITI must have done so at least 5 years before screening and must have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor  $>0.6$  BU/mL ( *$> 1.0$  BU/mL only for laboratories with an historical sensitivity cutoff for inhibitor detection of 1.0 BU/mL*) since ITI
- For patients to be enrolled into PK run-in cohort:
  - Current episodic treatment (FVIII or bypassing agents) at the time of entry into this study and documentation of details of episodic treatment for at least 24 weeks prior to entry into this study
- For patients to be enrolled into the expansion cohort:
  - Documentation of details of prophylactic or episodic treatment (FVIII or bypassing agents) and the number of bleeding episodes for at least 24 weeks prior to entry into this study
  - For patients on an episodic regimen,  $\geq 5$  bleeds in the prior 24 weeks, regardless of inhibitor status
- Adequate hematologic function, defined as a platelet count  $\geq 100,000/\mu\text{L}$  and hemoglobin  $\geq 8$  g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin  $\leq 1.5 \times$  age-adapted upper limit of normal (ULN) (excluding Gilbert's syndrome) and both AST and ALT  $\leq 3 \times$  age-adapted ULN at the time of screening, and no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine  $\leq 2.5 \times$  age-adapted ULN and creatinine clearance  $\geq 30$  mL/min by Cockcroft-Gault formula
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods that result in a failure rate of  $< 1\%$  per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ( $\geq 1$  year of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)

Examples of highly effective contraceptive methods with a failure rate of  $< 1\%$  per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of  $< 1\%$  per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods for contraception.

#### **4.1.2        Exclusion Criteria**

Patients who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing or planned ITI therapy; patients in whom ITI has failed will be eligible with a 72-hour washout period prior to the first emicizumab administration
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment
- Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Known HIV infection with CD4 counts  $< 200$  cells/ $\mu$ L  
HIV infection with CD4 counts  $\geq 200$  cell/ $\mu$ L permitted
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy

- Concomitant disease, condition, significant abnormality on screening evaluations or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator/co-investigator, pose an additional unacceptable risk in administering study drug to the patient
- Receipt of any of the following:
  - Emicizumab in a prior investigational study
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
  - A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
  - Any other investigational drug currently being administered or planned to be administered
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnancy or lactation or intention to become pregnant during the study
- Women with a positive serum pregnancy test result within 7 days prior to initiation of study drug

## **4.2 METHOD OF TREATMENT ASSIGNMENT**

The study is open label and consists of two cohorts and two parts: a PK run-in part and an expansion part. The first 6 patients will be assigned to the PK run-in part. An analysis of pharmacokinetics and safety will be conducted for these patients when the last patient has reached 6 weeks' treatment duration. Until this analysis, recruitment is paused and will be re-opened to recruit into the expansion cohort only if the safety and PK data of the PK run-in cohort support the study to proceed as planned.

## **4.3 STUDY TREATMENT**

The investigational medicinal product (IMP) for this study is emicizumab (RO5534262).

### **4.3.1 Formulation, Packaging, and Handling**

Emicizumab (RO5534262) will be supplied by the Sponsor as a sterile liquid for SC injection, contains no preservatives, and requires storage at 2–8° Celsius (do not freeze and protect from light). Each single-use vial contains 150 mg (nominal) of emicizumab at pH 6.0. The Drug Product is formulated as 150 mg/mL emicizumab in 150 mmol/L arginine, 0.5 mg/mL poloxamer 188, 20 mmol/L histidine–aspartic acid buffer (pH 6.0). For further information on the formulation and handling of emicizumab, see the Investigator's Brochure. In order to minimize the number of injections for patients in certain weight categories, the administration per single injection of up to 2 mL of drug product solution will be permitted. This will require pooling of emicizumab drug product solution from up to two 1-mL vials into a single syringe using a new transfer needle for each vial. The detailed procedure for vial pooling is described in the Instructions for Use.

## **4.3.2            Dosage, Dose Adjustments, Administration, and Compliance**

### **4.3.2.1            Subcutaneous Emicizumab**

The emicizumab regimen being tested is 3 mg/kg QW for 4 weeks followed by 6 mg/kg Q4W subcutaneously for 24 weeks. *For patients on 6 mg/kg Q4W who missed a dose, emicizumab should be administered as soon as possible but no later than 14 days from planned administration day. If more than 14 days have passed, the patient should take the next dose of emicizumab at the next scheduled date. In all cases, the study medication dosing will proceed in accordance with the original dosing schedule.*

All patients with suboptimal control of bleeding ( $\geq 2$  qualifying bleeds within 24 weeks on emicizumab treatment) may have the opportunity to increase their emicizumab maintenance dose to 3 mg/kg QW starting at Week 25, if they receive approval from the Medical Monitor (see Section 3.1.2). An increase of the emicizumab dose to 3 mg/kg QW can occur at the next scheduled emicizumab administration of the initial regimen (4 weeks from the last dose of a Q4W regimen).

The option to go back to a lower dose regimen as per investigator and patient discretion will remain and a decrease of the emicizumab dose from 3 mg/kg QW to a regimen that is 6 mg/kg Q4W or 3 mg/kg Q2W or 1.5 mg/kg QW is allowed. A change from 3 mg/kg QW to 6 mg/kg Q4W can be initiated 2 weeks after the last dose; whereas, a change from 3 mg/kg QW to 3 mg/kg Q2W or 1.5 mg/kg QW can be initiated at the next scheduled treatment of the QW dosing regimen.

For patients in the PK run-in cohort, all drug administrations in Weeks 1–25 will be conducted at the investigational site by an HCP. Patients who remain in the study after Week 25 will have the option to self-administer emicizumab at home if patient's ability to self-administer the study drug is documented in the source data, *except on days when PK assessment is planned (see Appendix 2). On these days, emicizumab should be administered at the investigational site after the PK sample has been drawn.*

Patients in the expansion cohort will also need to come to the site at all times of drug administration in Weeks 1–25 because predose PK and PD samples have to be drawn. Therefore, all SC injections will be performed at the site until Week 25 (unless mobile nursing [MN] is implemented; see Section 4.5). However, unassisted self-administration of the drug at the investigational site will be supported for patients in the expansion cohort, and patients remaining in the study after Week 25 might have the option to self-administer emicizumab at home. *On days when PK samples are to be collected (see Appendix 2), emicizumab should be administered at the investigational site after the PK sample has been drawn.*

Patients/caregivers will be required to complete in-person, instructional training on how to administer emicizumab as an SC injection. Patients/caregivers will be taught to perform the injections utilizing the Instructions for Use document. They will observe at least one SC injection performed by an HCP and will need to successfully administer at least one SC injection under an HCP's watch prior to starting unassisted self-administration.

Details on the devices to be used for study medication withdrawal from vial and SC injection are provided in the Pharmacy Manual.

Any overdose or incorrect administration of study drug will be determined from emicizumab data entered into the electronic, handheld device. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event electronic Case Report Form (eCRF).

Patients will be observed for a minimum of 60 minutes after the first three doses as described in Section 5.1.2.2. Patients/caregivers will be instructed on how to recognize signs/symptoms of hypersensitivity (including anaphylaxis) and obtain emergency care in the event of such reactions occurring. Each site will have the discretion to provide additional training or include additional observation (e.g., after the fourth and fifth doses), if deemed appropriate, and each patient/caregivers will be able to ask any question he or she may have prior to being deemed capable of performing SC emicizumab injections. If, despite additional training, the investigator determines that the patient/caregivers is unable to inject emicizumab, a trained and proficient caregiver or HCP should be identified to administer the SC injections.

Patients and/or the caregivers will be provided with alert cards, which they will be requested to carry at all times. These will include guidance on recognizing signs/symptoms of thromboembolic events or allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care.

The Sponsor is currently evaluating the option to provide MN support during the study for patients in the expansion cohort (see Section 4.5).

#### **4.3.3 Investigational Medicinal Product Accountability**

Emicizumab, the only IMP in this study, is required for completion of this study and will be provided by the Sponsor. Accountability for each vial is required throughout the study. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.



IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

#### **4.3.4 Post-Study Access to Emicizumab**

The Sponsor will offer post-study access to the study drug (emicizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for patients with hemophilia A
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for hemophilia A
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

[http://www.roche.com/policy\\_continued\\_access\\_to\\_investigational\\_medicines.pdf](http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf)

#### **4.4 CONCOMITANT THERAPY**

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. All such

medications should be reported to the investigator and recorded on the Concomitant Medications eCRF page. Medications given to treat a bleed (e.g., rFVIIa or aPCC) will be reported only via the electronic, handheld device, except for FVIII taken in the week prior to starting emicizumab by patients without inhibitors to FVIII who will continue their prior FVIII prophylaxis until the second loading dose of emicizumab. For these patients only, FVIII treatments taken in the week prior to the first dose of emicizumab will be recorded on the Concomitant Medication eCRF page.

#### **4.4.1      Permitted Therapy**

Concomitant use of the following drugs and therapies will be permitted:

- For patients in the expansion cohort who are on FVIII prophylaxis, they may continue their regular FVIII prophylaxis until the second emicizumab loading dose in order to avoid bleeds before adequate emicizumab level is reached. Concomitant routine FVIII prophylaxis is not otherwise permissible during the study.
- Drugs intended to control bleeds, including FVIII concentrates (non-inhibitor patients) or rFVIIa (inhibitor patients), should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve hemostasis may be lower than the FVIII or bypassing agent doses used prior to starting the study.

Caution should be taken for patients who are using rFVIIa (e.g., consideration of using no more than 90 µg/kg rFVIIa as an initial dose).

*Use of aPCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds.* In the event that aPCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed with no more than 50 units/kg of aPCC to be administered as an initial dose. For patients receiving aPCC prior to study entry, a washout period of 72 hours prior to first emicizumab dosing is required.

Other bypassing agents (e.g., Byclot) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 µg/kg of Byclot). For patients receiving Byclot prior to study entry, a washout period of 72 hours prior to first emicizumab dosing is required.

Exact dose and schedule of FVIII or bypassing agents should be discussed with patients at the beginning and throughout the study. Repeated dosing of FVIII, rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision and consideration should be given to verifying bleeds prior to repeated dosing. For rFVIIa, aPCC, and other bypassing agents, laboratory

monitoring by additional local and central laboratory assessments should be performed as per the schedule of assessments (see [Appendix 1](#)).

- *Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab.*
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, and so on, that are not considered to result in systemic exposure
- Drugs to treat an existing medical condition ongoing at study entry that do not violate the eligibility criteria (e.g., anti-retroviral therapy for HIV infections)

#### **4.4.2      Prohibited Therapy**

Use of the following therapies is prohibited for at least 4 weeks prior to initiation of study treatment, during the study, and until last observation (except for aPCC and Byclot that require a washout period of 72 hours prior to study treatment and can be used for the treatment of breakthrough bleeds during the study as per guidance in [Section 4.4.1](#)):

- Drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs *that are not selective or preferential COX-2 inhibitors*, or anticoagulants [other than to flush, dwell, or de-clot a venous access device]) but excluding drugs intended to control bleeding episodes or used in the context of minor surgery (e.g., tooth extraction) or injuries (e.g., concussion) to prevent deterioration
- Systemic immunomodulators (e.g., rituximab, interferon) other than anti-retroviral therapy
- Elective surgery (excluding minor procedures such as tooth extraction or incision and drainage as well as emergency surgeries)
- Use of other investigational drugs
- Use of aPCC for short-term prophylaxis
  - Use of concomitant prophylactic regimen with FVIII or rFVIIa (short-term prophylaxis [e.g., around the time of surgery], however, is permitted)
- *Use of anti-fibrinolytics in conjunction with aPCC or Byclot*

If prohibited therapy is administered for any reason, it should be recorded on the eCRF. If prohibited treatment is prescribed or considered medically necessary, the Medical Monitor should be consulted to discuss any changes in the benefit/risk and determine whether the patient should continue on the study.

#### **4.5      STUDY ASSESSMENTS**

See [Appendix 1](#) for the schedule of assessments performed during the study.

The Sponsor may consider providing MN support. If the Sponsor decides to provide MN support, at applicable sites and for patients in the expansion cohort only, certain study

assessments during the study may be performed by an MN professional at the patient's home or another suitable location, such as his or her school or office, to improve access and convenience for patients participating in the study. The Sponsor may select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor will be responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional.

#### **4.5.1 Informed Consent Forms and Screening Log**

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. For adolescents (i.e., 12–17 years of age), an Informed Assent Form will be completed instead. Parents or legally authorized representatives of adolescents will also complete an Informed Consent Form.

All screening evaluations must be completed within 4 weeks prior to the first dose and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

#### **4.5.2 Medical History and Demographic Data**

Medical history includes clinically significant diseases, procedures, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to enrollment (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies). Finally, all bleed information (i.e., start date, cause, type, location), number of school/work days missed, and number of days hospitalized during the 24 weeks prior to study entry should be documented.

Demographic data will include age, sex, and self-reported race and ethnicity.

#### **4.5.3 Physical Examinations**

A complete physical examination should include but not necessarily be limited to the evaluation of head, eye, ear, nose, and throat and include cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems, height, and weight. Any abnormality identified during screening should be recorded on

the General Medical History and Baseline Conditions eCRF. Subsequently, a targeted (i.e., musculoskeletal, dermatological) and/or symptom-driven examination should be conducted as noted in the schedule of assessments or as clinically indicated. New or worsened abnormalities from screening should be recorded as adverse events, if appropriate.

#### **4.5.4 Vital Signs**

Vital signs will include measurement of heart and respiratory rate, temperature, and systolic and diastolic blood pressure and should be recorded before study drug administration. Frequency of vital sign assessments should follow the schedule of assessments but may also be taken anytime as unscheduled assessments as judged by the investigator.

#### **4.5.5 Laboratory, Biomarker, and Other Biological Samples**

Local laboratory assessments will be performed as indicated on the schedule of assessments. On days of study drug administration, laboratory samples should be drawn before the administration of study drug. In the PK run-in, no deviation from defined drug administration visits is allowed until Week 25. Deviations from the schedule of assessments of  $\pm 2$  days are acceptable after Week 25 in the PK run-in cohort. For the expansion cohort, deviations from the schedule of assessments of  $\pm 2$  days are acceptable; however, predose PK and PD sample collection and drug administration should coincide.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width)
- Serum chemistries (sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase)
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and within 7 days prior to initiation of study medication, if applicable

Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

*In the event of use of a bypassing agent, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent administration so the investigator may monitor for potential thromboembolic events and thrombotic microangiopathy: platelet count, serum creatinine, LDH, and schistocytes. A plasma*

sample should also be provided for local and central laboratory monitoring of prothrombin fragment 1+2, fibrinogen and D-dimer. If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents. If applicable, laboratory results should be recorded in the *Following Treatment with Bypassing Agents eCRF form*.

The following samples will be sent to the Sponsor or a designee for centralized analysis:

- Plasma samples for PK analysis
- Plasma samples for immunogenicity assessment (anti-drug antibody [ADA])
- Plasma samples for anti-FVIII antibody measurement (inhibitor titer) will be sent to the Sponsor throughout the study, with the exception of the test needed at screening for patients who do not have a documented inhibitor test result within 4 weeks prior to enrollment, per inclusion criteria (see Section 4.1.1).
- Plasma for PD and exploratory PD biomarker assessments (aPTT, PT, FVIII activity, thrombin generation, FIX:Ag, FX:Ag, and others as listed in [Appendix 2](#)).
- *Plasma aliquot for central lab assessment of fibrinogen, D dimer, and prothrombin fragment 1.2, collected after administration of bypassing agents (as listed in [Appendix 1](#), Schedule of Assessments, in the footnotes). This sample is addition to the local laboratory monitoring after bypassing agent use as described above.*

In certain instances, blood draws may be performed by an MN professional (see Section 4.5).

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling Manual.

#### **4.5.5.1 Pharmacokinetic Samples**

Blood samples for determination of plasma concentrations of emicizumab will be collected as specified in the schedule of assessments (see [Appendix 1](#)) and will be sent to the Sponsor or a designee for centralized analysis.

Emicizumab plasma concentrations will be measured by a specific and validated enzyme-linked immunosorbent assay (ELISA) method. For blood draws, when the PK assessment is scheduled for the same nominal time as another scheduled assessment, the PK sample will take precedence.

Details on sampling procedures, sample storage, and shipment are given in the Sample Handling Manual.

#### **4.5.6      Electrocardiograms**

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of assessments (see [Appendix 1](#)).

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The following parameters will be obtained (and reported by the instrument): QT, RR, HR, QTcB, QTcF, PR and QRS and T- and U-wave morphology. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

Any ECG changes that are associated with symptoms or lead to a change in study treatment or concomitant treatment, or discontinuation from study treatment must be reported as an adverse event on the adverse event eCRF. The investigator or designee must review, sign, and date all ECG tracings. The ECG may be repeated if investigator deems it appropriate. Paper copies will be kept as part of the patient's permanent study file at the site. During the study, the Sponsor may request copies of ECGs to be submitted to the Sponsor or a Central Vendor. Centralized ECG reading and interpretations will not be performed unless safety concerns arise.

#### **4.5.7      Patient-Reported Outcomes**

A data collection modality via an electronic, handheld device will be employed. To capture PRO data during study treatment, patients will complete the HRQoL, health status, preference questionnaires, and questions related to the number of missed days of school or work electronically at study sites during the specified visits. The instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a pre-specified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the electronic, handheld device vendor. The data can be accessed securely by appropriate study personnel via the Internet. In case the device is not available, paper questionnaires might be used.

#### **HRQoL**

The Haem-A-QoL and the Haemo-QoL-SF will be used to measure HRQoL in adults and adolescents, respectively (see [Appendix 5](#) and [Appendix 6](#)). The Haem-A-QoL was designed for adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, view, sport and leisure time, work and school, dealing, treatment, future, family planning, and relationships/partners) and a scale

representing total score. Items are rated along 5 response options, although for some items there is also a 'not applicable' option ([von Mackensen and Gringeri 2005](#); [2010](#)).

The Haemo-QoL has been developed in a series of age-related questionnaires to measure health-related quality of life in children and adolescents with hemophilia ([Bullinger et al. 2002](#); [von Mackensen and Bullinger 2004](#); [Pollak et al. 2006](#)). These versions include a 77-item long form, a 35-item as well as a 16-item short form, and an 8-item index form. The short version for older children (8–17 years) containing 35 items was selected for adolescents in this study. This version covers nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated with five respective response options: never, seldom, sometimes, often, and always. Higher scores for both HRQoL measures are indicative of poorer HRQoL.

### **Health Status**

The EQ-5D-5L (see [Appendix 7](#)), is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis ([EuroQol Group 1990](#); [Brooks 1996](#); [Herdman et al. 2011](#); [Janssen et al. 2013](#)). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D-5L will be utilized in this study for economic modeling.

### **Missed Days of School or Work**

Patients will also be asked to document the number of days of school or work missed in the previous 4 weeks at the timepoints outlined in the schedule of assessments (see [Appendix 1](#)).

### **Patient Preference**

Patient preference will be assessed through the Preference Survey, which asks patients to report which treatment they would prefer to continue to receive after having been treated with IV FVIII or bypassing agents (episodic or prophylaxis) prior to study entry and SC emicizumab during the study. Patients who express a preference are then asked to identify which reasons may have influenced their decision and indicate the top three reasons for their choice. Patients will complete this questionnaire at Week 17 on emicizumab.



#### **4.5.8      Bleed Definitions**

##### **Definition of a Bleed**

For the purpose of the efficacy analyses, a standardized definition of bleed, adapted from criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis, and similar to that used in a recent clinical study, will be utilized in this study ([Blanchette et al. 2014](#); [Mahlangu et al. 2014](#)).

- An event is considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding (e.g., pain, swelling, etc.). An additional definition of all reported bleeds (irrespective of treatment with coagulation factors) will be applied for a separate analysis.
- Bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are  $\leq 72$  hours apart, are considered the same bleed.
- Any injection to treat the bleed, taken  $> 72$  hours after the preceding injection, is considered the first injection to treat a new bleed at the same location.
- Any bleed at a different location is considered a separate bleed regardless of time from last injection.

##### **Definitions of Bleed Sites**

- Target joints: defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of  $\geq 3$  bleeds into the same joint over the last 24 weeks prior to study entry)
- Joint bleeds *are defined as bleeds with bleed type “joint bleed” reported via the bleed/medication questionnaire with at least one of the following symptoms:*
  - Increasing swelling or warmth of the skin over the joint
  - Increasing pain
  - Progressive loss of range of motion or difficulty in using the limb as compared with baseline
- Muscle bleeds (sites as per the bleed/medication questionnaire)
- Other (sites as per the bleed/medication questionnaire)

##### **Definitions of Bleed Types**

In addition, the assessment of a bleed will be separated into spontaneous bleeds, traumatic bleeds and bleeds related to procedure/surgery. Both spontaneous bleeds (i.e., the occurrence of hemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, “strenuous” activity, or “overuse”) will be collected.

- Spontaneous bleeds: Bleeds should be classified as spontaneous if a patient records a bleed when there is no known contributing factor such as definite trauma, antecedent “strenuous” activity or “overuse.” The determination of what constitutes “strenuous” or “overuse” will be at the discretion of the patient. For

example, light jogging may be considered “non-strenuous” while sprinting may be considered “strenuous,” lifting of weights for a short period of time may be considered “moderate use” while repetitive weightlifting may be considered “overuse.”

- Traumatic bleeds: Bleeds should be classified as traumatic if a patient records a bleed when there is a known or believed reason for the bleed. For example, if a patient were to exercise “strenuously” and then have a bleed in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed because, although no injury occurred, there was antecedent “strenuous” activity. Bleeds subsequent to injuries would certainly be classified as traumatic.
- Bleeds related to procedure/surgery: such as hematomas resulting from any surgeries or invasive procedures (e.g., tooth extractions, venipuncture, or SC drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy, etc.) would not be counted as bleeds. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

Patients (or their legally authorized representative) will complete a bleed/medication questionnaire weekly and whenever a bleed occurs via an electronic, handheld device. For each bleeding episode, they will provide information on the above topics as well as on the medication used to treat the bleed. Hemophilia medications that were taken will also be collected through the bleed/medication questionnaire. If the electronic, handheld device is not available, a paper questionnaire might be used. Investigators will review the bleed and bleed medication data as per the schedule of assessments (see [Appendix 1](#)) and have the option to correct or complete these in agreement with the patient via a Data Request Form process or via a Web-based portal, once implemented. The Sponsor will have view-access only but will do a review of the bleed and bleed medication data as per the Medical Data Review Plan.

## **4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION**

### **4.6.1 Patient Discontinuation**

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient’s inability or unwillingness to comply with protocol requirements (non-compliance despite appropriate education measures taken by the clinical site)

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients participating in the PK run-in cohort who withdraw from the study will be replaced if they withdraw prior to being in the study for 6 weeks. Patients participating in the expansion cohort who withdraw at any time will not be replaced.

#### **4.6.2            Study Treatment Discontinuation**

Patients must discontinue study treatment if they experience the following:

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient via the electronic handheld device until the safety follow-up visit (24 weeks after last study drug administration).

#### **4.6.3            Study and Site Discontinuation**

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

### **5.                ASSESSMENT OF SAFETY**

#### **5.1                SAFETY PLAN**

Emicizumab is currently in clinical development and is not approved. Thus, the complete safety profile is not known at this time. The safety plan for this study is

designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below. Please refer to the RO5534262 (Emicizumab) Investigator's Brochure for a complete summary of safety information.

### **5.1.1      Patient Selection**

The inclusion and exclusion criteria in this study are designed to select patients who are not at increased risk based on the current understanding of the investigational medication. See Section [4.1.1](#) and Section [4.1.2](#) for full inclusion and exclusion criteria, respectively.

### **5.1.2      Risks Associated with Emicizumab**

#### **5.1.2.1      Injection-Site Reactions**

In the completed and ongoing Japanese studies, injection-site reactions have been observed in some patients with hemophilia A. These local injection-site reactions included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, injection-site pain, and injection-site pruritus. All local injection-site reactions were of mild intensity. Further details of the observed injection-site reactions are available in the Investigator's Brochure.

Directions for emicizumab administration should be followed as outlined in Section [4.3.2](#).

#### **5.1.2.2      Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction**

Since emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. In completed and ongoing clinical studies of emicizumab, no severe hypersensitivity reactions have been reported. These events should be reported as serious adverse events or adverse events of special interest as described in Sections [5.2.2](#) and [5.2.3](#), respectively.

HCPs administering the study medication in the clinic must be trained in the appropriate administration procedures, be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions, and should be familiar with Sampson's criteria for defining anaphylaxis ([Sampson et al. 2006](#); see [Appendix 3](#) and [Appendix 4](#)). HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should any of these reactions occur.

For patients with a previous history of a clinically significant hypersensitivity reaction, after each of the first three doses, the site will call the patient 24 hours after each dose to assess the status of the patient. Additional precautions following each of these doses may also be considered, including having an extended observation period or IV access prior to dosing, etc. The investigator may include these or other precautions, as deemed appropriate.

### 5.1.2.3 Hypercoagulation and Thromboembolic Events

As of *April 2017*, there have been 2 *serious* thromboembolic events reported in 2 patients with hemophilia A with inhibitors while receiving emicizumab in Study BH29884.

[REDACTED]

These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3. HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain or swelling, etc.) and ensure that they understand the importance of seeking appropriate medical attention. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should thromboembolism be suspected.

### 5.1.2.4 Thrombotic Microangiopathy

Thrombotic microangiopathy is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, etc. As of *April 2017*, 3 cases of TMA were observed in a Phase III clinical study involving patients with hemophilia A with inhibitors while receiving emicizumab. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

For more details please refer to Investigator  
Brochure.

These events should be reported as serious adverse events or adverse events of special interest, see Section 5.2.3.

#### **5.1.2.5      *Life-Threatening Bleeding Due to Unreliable Standard Coagulation Tests and Inhibitor Assays in the Setting of Emicizumab***

*Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis (see Section 5.1.4 ). Due to the long t1/2 of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose.*

*There is a risk of life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab in the market setting by practitioners, particularly for emergency care practitioners.*

*Emicizumab's mechanism of action and resulting interference was clearly demonstrated in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials also demonstrated the effects of emicizumab on laboratory tests. However, as of April 2017, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab were observed.*

### 5.1.3 Management of Specific Adverse Events

**Table 1 Guidelines for Management of Specific Adverse Events**

Event	Actions to Be Taken
Injection-Site Reaction	<ul style="list-style-type: none"> <li>• Injection-site reactions should be treated as clinically indicated.</li> <li>• Emicizumab should not be injected into areas where the skin is red, bruised, tender, or hard or into areas where there are moles or scars.</li> <li>• In the clinic setting, patients will be monitored for signs of injection-site reactions in the period immediately following injections. Patients will be given guidance on reporting injection-site reactions when administering drug at home or after they leave the clinic.</li> </ul>
Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction	<ul style="list-style-type: none"> <li>• Suspected cases should be fully evaluated and treated as clinically indicated.</li> <li>• Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) and resuscitation equipment must be available for immediate use during the initial administrations in the infusion center, clinic, or hospital.</li> <li>• If a patient has symptoms of anaphylaxis or severe hypersensitivity, administration of study drug must be immediately stopped and treatment of the reaction be initiated.</li> <li>• The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if and when the patient should resume taking emicizumab and discuss the patient's continued study participation. If patient continues in the study, the next two scheduled doses must be in a monitored setting with at least a 60-minute observation period and resuscitation treatment immediately available. After each of these two doses in the clinic, the site will call the patient 24 hours after each dose to assess status of the patient.</li> <li>• Investigators may order any pertinent laboratory tests, including an unscheduled anti-drug antibody, in the event any of these reactions occur.</li> </ul>
Hypercoagulation and Thromboembolic Events	<ul style="list-style-type: none"> <li>• Please see Section 4.5.5 for guidance on required laboratory monitoring <i>in the event of use of bypassing agents</i>.</li> <li>• HCPs should be vigilant for patients who exhibit signs/symptoms consistent with thromboembolic events and immediately begin work-up and treatment, as per local guidelines.</li> <li>• If a patient has a thromboembolic event, further administration of study drug should be interrupted. Decision to resume emicizumab after a thromboembolic event must be discussed with and approved by the Medical Monitor.</li> </ul>
Thrombotic microangiopathy	<ul style="list-style-type: none"> <li>• Please see Section 4.5.5 for guidance on required laboratory monitoring <i>in the event of use of bypassing agents</i>.</li> <li>• HCPs should be vigilant for patients who exhibit signs/symptoms consistent with TMA and immediately begin work-up and treatment, as per local guidelines.</li> <li>• If a patient has a TMA event, further administration of study drug should be interrupted. Decision to resume emicizumab after an event of TMA must be discussed with and approved by the Medical Monitor.</li> </ul>



**Table 1 Guidelines for Management of Specific Adverse Events (cont.)**

Event	Actions to Be Taken
Coagulation Disorder and Risk of Bleeding	<ul style="list-style-type: none"><li>• HCPs should be vigilant for abnormal or unusual bleeding tendencies. Coagulation tests or other work-up may be indicated if judged to be appropriate by the investigator. If bleeding is observed, appropriate action as per local guidelines must be taken immediately.</li></ul>

HCP = healthcare provider; TMA = thrombotic microangiopathy.

#### **5.1.4      Interpretation of Coagulation Assays for Patients Receiving Emicizumab**

Emicizumab interacts with standard laboratory assays used in the management of patients with hemophilia A. In one-stage assays, emicizumab is associated with a supra-physiologically short time to clot formation and thus normalization of aPTT at subtherapeutic levels and an overestimation of true FVIII activity. Emicizumab is not recognized or neutralized by FVIII inhibitors, and therefore cannot be detected by a functional test such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting-based readout. Emicizumab activity cannot be detected by chromogenic assays using purified bovine coagulation proteins and can only be detected using an assay composed of human proteins. See the RO5543262 [Emicizumab] Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

### **5.2            SAFETY PARAMETERS AND DEFINITIONS**

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).

#### **5.2.1      Adverse Events**

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section [5.3.5.10](#)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### **5.2.2      Serious Adverse Events (Immediately Reportable to the Sponsor)**

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.11](#))
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to the World Health Organization [WHO] toxicity grading scale; see Section [5.3.3](#)); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#) for reporting instructions).

### **5.2.3      Adverse Events of Special Interest (Immediately Reportable to the Sponsor)**

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). These may include suspected or confirmed cases. Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Sampson's Criteria in Appendix 3 and Appendix 4)
- Thromboembolic events
- Microangiopathic hemolytic anemia or thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)

## **5.3              METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS**

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### **5.3.1      Adverse Event Reporting Period**

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

**After informed consent** has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

**After initiation of study drug**, all adverse events will be reported until the patient completes his or her last study visit. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

### **5.3.2      Eliciting Adverse Event Information**

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

### **5.3.3      Assessment of Severity of Adverse Events**

The WHO toxicity grading scale (see Appendix 3) will be used for assessing adverse event severity (WHO 2003). Table 2 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

**Table 2      Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale**

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

### **5.3.4      Assessment of Causality of Adverse Events**

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)

- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

### **5.3.5      Procedures for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### **5.3.5.1      Injection-Site Reactions**

Local adverse events that occur within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as an “injection-site reaction” on the Adverse Event eCRF. Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. If a patient experiences both a local and systemic reaction to the same administration of study drug, each reaction should be recorded separately on the Adverse Event eCRF. Only for local injection-site reactions should the dedicated Injection-Site Reaction eCRF be used to capture the individual signs/symptoms.

#### **5.3.5.2      Diagnosis versus Signs and Symptoms**

For adverse events, other than injection-site reactions (see Section [5.3.5.1](#)), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

### **5.3.5.3 Adverse Events That Are Secondary to Other Events**

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

### **5.3.5.4 Persistent or Recurrent Adverse Events**

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

### **5.3.5.5 Abnormal Laboratory Values**

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin  $5 \times \text{ULN}$  associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

### **5.3.5.6 Abnormal Vital Sign Values**

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).



### 5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ( $> 3 \times$  baseline value) in combination with either an elevated total bilirubin ( $> 2 \times$  ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event of special interest the occurrence of either of the following:

- Treatment-emergent ALT or AST  $> 3 \times$  baseline value in combination with total bilirubin  $> 2 \times$  ULN (of which  $\geq 35\%$  is direct bilirubin)
- Treatment-emergent ALT or AST  $> 3 \times$  baseline value in combination with clinical jaundice in the absence of cholestasis or other cause of hyperbilirubinemia

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

### 5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of hemophilia A.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of hemophilia A, "hemophilia A progression" should be recorded on the Adverse Event eCRF.

### 5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

#### **5.3.5.10 Lack of Efficacy or Worsening of Hemophilic Bleeds**

At any time during the study an unexpected worsening of hemophilia-related bleeding, as judged by the investigator, should be recorded as an adverse event; for example, increased severity (e.g., increased number of coagulation factor doses required to stop bleeds compared with before study entry) or frequency of bleeds. Hemophilia worsening should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia"). A clinically significant bleed (i.e., intracranial, retroperitoneal) does not by itself constitute loss of efficacy, unless it is associated with features indicating worsening of the underlying hemophilia phenotype. Events that are clearly consistent with the expected pattern of the underlying disease should not be recorded as adverse events. These data will be reflected in efficacy assessment data only.

#### **5.3.5.11 Hospitalization or Prolonged Hospitalization**

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

*An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:*

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The patient has not experienced an adverse event

*An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:*

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

#### **5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration**

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing or drug administration error of emicizumab are available, as no such instances have been observed to date. To minimize the risk of errors associated with future home administration of emicizumab, data related to medication errors with observed patient/caregivers administration of emicizumab at the site by the investigator and/or clinical staff will be recorded and corrected at the time of occurrence.

#### **5.3.5.13 Patient-Reported Outcome Data**

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

### **5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR**

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

#### **5.4.1            Emergency Medical Contacts**

##### **Medical Monitor Contact Information for all sites**

Medical Monitor [REDACTED], Ph.D.

Telephone No.: [REDACTED]

Mobile Telephone No.: [REDACTED]

Roche Medical Responsible: [REDACTED], M.D.

Telephone No.: [REDACTED]

Mobile Telephone No.: [REDACTED]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

#### **5.4.2            Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest**

##### **5.4.2.1        Events That Occur prior to Study Drug Initiation**

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators.

##### **5.4.2.2        Events That Occur after Study Drug Initiation**

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 24 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section [5.6](#).

### **5.4.3      Reporting Requirements for Pregnancies**

#### **5.4.3.1      Pregnancies in Female Patients**

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### **5.4.3.2      Pregnancies in Female Partners of Male Patients**

Although embryo-fetal development studies are not available, condom use will not be required in male patients enrolled in the study because the margin between the minimal anticipated biological effect level (MABEL) plasma concentration (7 ng/mL) and the estimated maternal  $C_{\max}$  (at both 1.5 and 3 mg/kg QW dosing regimens) is greater than 10-fold ([Banholzer et al. 2012](#)). At this time, very little emicizumab is thought to transfer into semen, and there are no known reproductive risks to female partners of male patients treated with emicizumab, so contraception use by male patients is not required for participation in the study. Therefore, no proactive collection of pregnancy information for female partners of male patients treated with emicizumab will be required.

#### **5.4.3.3      Abortions**

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

#### **5.4.3.4 Congenital Anomalies/Birth Defects**

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

### **5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS**

#### **5.5.1 Investigator Follow-Up**

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

#### **5.5.2 Sponsor Follow-Up**

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

### **5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD**

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 24 weeks after the last dose of study drug or rollover to an extension study), if the event is believed to be related to prior study drug treatment.

These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or e-mail address provided to investigators.

## **5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES**

The Sponsor will promptly evaluate all serious adverse events (see Section 5.2.2) and adverse events of special interest (see Section 5.2.3) against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- RO5534262 (Emicizumab) Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

## **6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN**

No formal hypothesis testing is planned for this study. All analyses will be descriptive. The 6 run-in patients will be analyzed separately from the expansion cohort.

### **6.1 DETERMINATION OF SAMPLE SIZE**

The sample size of 6 patients for the PK run-in cohort is considered appropriate to assess pharmacokinetics and safety to allow for an informed decision to open the subsequent expansion cohort with 40 additional patients.

The overall sample size of 40 patients in the expansion cohort is based primarily on clinical considerations taking into account the limited number of patients with hemophilia A. *A sample size of 40 patients is expected to provide statistically robust point estimates with meaningfully narrow confidence intervals.*

### **6.2 SUMMARIES OF CONDUCT OF STUDY**

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

## **6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS**

Demographic and baseline characteristics (including age, sex, etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

## **6.4 EFFICACY ANALYSES**

The efficacy objective is to evaluate the clinical effect of 6 mg/kg emicizumab Q4W based on the number of bleeds over time.

### **6.4.1 Efficacy Endpoints**

The key efficacy objective is to characterize the efficacy of 6 mg/kg emicizumab Q4W based on the number of bleeds over time for patients in the expansion cohort.

The analyses will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of the time that each patient stays in the study included as an offset in the model.

The number of bleeds will be also annualized (Annualized Bleeding Rate—ABR) for each patient using the following formula:

$$ABR = \left( \frac{\text{Number of bleeds during the efficacy period}}{\text{Total number of days during the efficacy period}} \right) \times 365.25$$

In case the negative binomial model does not converge the above formula will be used as the sole method of analysis.

The clinical effect of prophylactic emicizumab on the number of bleeds, joint bleeds, target joint bleeds, spontaneous bleeds and all bleeds (i.e., those treated and untreated with coagulation factors) over time will be evaluated (see Section [2.2.1](#)).

The number of bleeds, sites of bleeds, and types of bleeds will be summarized for all patients and listed for each patient individually. Several exploratory analyses will be conducted to characterize the type, location, duration, frequency, and pattern of bleeds. For continuous endpoints, descriptive statistics will be calculated and categorical endpoints will be characterized through frequency tables.

The primary final analysis will be performed 24 weeks after the last enrolled patient started treatment or has withdrawn prematurely, whichever occurs first.

A detailed description of the statistical methods that will be used for the efficacy analyses will be provided in the Statistical Analysis Plan.



#### **6.4.2      Patient-Reported Outcomes**

Scale scores for the Haemo-QoL-SF and the Haem-A-QoL will be calculated for each assessment, with change scores being examined for the assessments over the course of 24 weeks. These will be summarized descriptively.

The proportion of patients preferring emicizumab after 17 weeks of treatment will be presented along with the reasons for that choice. Summary statistics of the number of days away from school and days hospitalized will be presented.

### **6.5            SAFETY ANALYSES**

The safety analyses population will be based on all patients who received at least one administration of emicizumab. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts), ECGs, vital signs, ADAs, and de novo anti-FVIII inhibitors.

To evaluate the overall safety of emicizumab, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade.

For clinical laboratory data, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale ([WHO 2003](#)).

### **6.6            PHARMACOKINETIC ANALYSES**

#### **PK Run-In Cohort**

PK parameters of emicizumab will be estimated using non-compartmental methods after the first and the sixth injection and include:

- $T_{max}$ : Time to maximum observed plasma concentration
- $C_{max}$ : Maximum observed plasma concentration
- $AUC_{\tau}$ : Area under the plasma concentration–time curve over a dosing interval
- $AUC_{0-inf}$ : Area under the plasma concentration–time curve between time zero (predose) extrapolated to infinity (only for the first injection)
- $t_{1/2}$ : Apparent terminal half-life
- $CL/F$  and  $CL_{ss}/F$ : Apparent Clearance

Concentration data and calculated PK parameters for emicizumab will be presented in individual listings, summary tables (including descriptive statistics: mean, geometric means, medians, ranges, standard deviations, and coefficients of variation) and graphs (including concentration versus time plots on linear and semi-logarithmic scales) as appropriate.

## **Expansion Cohort**

For all patients, predose (trough) plasma concentrations of emicizumab will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, gender, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies and completed Phase III studies. These analyses will be reported in a dedicated report.

## **6.7 IMMUNOGENICITY ANALYSES**

The immunogenicity analyses will include patients with at least one predose and one postdose ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e.,  $\geq 0.60$  titer units) than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

## **6.8 EXPLORATORY ANALYSES**

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

## **6.9 INTERIM ANALYSIS**

### **6.9.1 Planned Interim Analysis**

An analysis of pharmacokinetics and safety will occur when the first 6 patients have been on treatment for 6 weeks. On the basis of the results for pharmacokinetics and safety (e.g.,  $\geq$  lower limit of 95% CI of the predicted mean PK profile, no severe unexpected safety findings), the study will proceed with the expansion cohort.

This analysis will be conducted by a Roche internal group of representatives from Clinical Pharmacology, Clinical Science, Clinical Safety and Statistics; no formal IMC will be set up.

### **6.9.2            Optional Interim Analysis**

Additional interim data reviews may be performed at various timepoints to support regulatory submissions.

## **7.                DATA COLLECTION AND MANAGEMENT**

### **7.1                DATA QUALITY ASSURANCE**

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

### **7.2                ELECTRONIC CASE REPORT FORMS**

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

### **7.3                ELECTRONIC PATIENT-REPORTED OUTCOME DATA**

Patient-reported data will be collected electronically with use of electronic devices. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted electronically in real-time to a

centralized database at the vendor of the electronic handheld devices. The data from the electronic devices are available for view access only via secure access to a Web portal provided by the vendor. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor. The Sponsor will receive all data entered by patients on the electronic handheld devices and all relevant study documentation.

Once the study is complete, the data, audit trail, and study and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

## **7.4 SOURCE DATA DOCUMENTATION**

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, electronic handheld device records, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section [7.6](#).

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

## **7.5 USE OF COMPUTERIZED SYSTEMS**

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## **7.6 RETENTION OF RECORDS**

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

## **8. ETHICAL CONSIDERATIONS**

### **8.1 COMPLIANCE WITH LAWS AND REGULATIONS**

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

### **8.2 INFORMED CONSENT**

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms")

before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

### **8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE**

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

### **8.4 CONFIDENTIALITY**

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

### **8.5 FINANCIAL DISCLOSURE**

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

## **9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION**

### **9.1 STUDY DOCUMENTATION**

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

### **9.2 PROTOCOL DEVIATIONS**

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

### **9.3 SITE INSPECTIONS**

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

### **9.4 ADMINISTRATIVE STRUCTURE**

This global study will enroll 46 patients.

For the PK run-in only sites will be selected that have proven via feasibility that they can comply with the extensive PK/PD sampling requirements and the schedule of assessments without any deviations.

Drug assignment will be performed by an IxRS, which will also manage emicizumab inventory for all sites globally.

PROs will be captured on an electronic handheld device provided by a third-party vendor for all patients globally.

Central laboratories will be used for a subset of laboratory assessments specified in Section [4.5.5](#).



## **9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS**

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

*[http://www.roche.com/roche\\_global\\_policy\\_on\\_sharing\\_of\\_clinical\\_study\\_information.pdf](http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf)*

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

## **9.6                    PROTOCOL AMENDMENTS**

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

## 10. REFERENCES

- Ahnstrom J, Berntorp E, Lindvall K, et al. A 6-year follow-up of dosing, coagulation factor levels and bleedings in relation to joint status in the prophylactic treatment of haemophilia. *Haemophilia* 2004;10:689–97.
- Antun A, Monahan PE, Manco-Johnson MJ, et al. Inhibitor recurrence after immune tolerance induction: a multicenter retrospective cohort study. *J Thromb Haemost* 2015;13(11):1980–8.
- Banholzer ML, Buergin H, Wandel C, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partners. *J Transl Med* 2012;10:129.
- Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost* 2014;12:1935–9.
- Brooks R. EuroQol: the current state of play. *Health Policy* 1996 Jul;37(1):53–72.
- Brown TM, Lee WC, Joshi AV, et al. Health-related quality of life and productivity impact in haemophilia patients with inhibitors. *Haemophilia* 2009;15:911–7.
- Bullinger M, Von Mackensen S, Fischer K, et al. Pilot testing of the Haemo-QoL quality of life questionnaire for haemophiliac children in six European countries. *Haemophilia* 2002;8:47–54.
- Cimino E, Linari S, Malerba M, et al. Patient preference and ease of use for different coagulation factor VIII reconstitution device scenarios: a cross-sectional survey in five European countries. *Patient Preference and Adherence* 2014;8 1713–20.
- Collins PW, Björkman S, Fischer K, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. *J Thromb Haemost* 2010;8:269–75.
- Collins PW, Young G, Knobe K, et al. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial. *Blood* 2014;124(26):3880–6.
- De Moerloose P, Urbancik W, Van Den Berg HM, et al. A survey of adherence to haemophilia therapy in six European countries: results and recommendations. *Haemophilia* 2008;14(5):931–8.
- Den Uijl IE, Mauser-Bunschoten EP, Roosendaal G, et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? *Haemophilia* 2011;17(6):849–53.
- Eton DT, Elraiyah TA, Yost KJ, et al. A systematic review of patient-reported measures of burden of treatment in three chronic diseases. *Patient Relat Outcome Meas* 2013;4:7–20.

- EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990 Dec;16(3):199–208.
- Ewenstein BM, Valentino LA, Journeycake JM, et al. Consensus recommendations for use of central venous access devices in haemophilia. *Haemophilia* 2004;10:629–48.
- Fischer K, Steen K, Carlsson P, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. *Blood* 2013;122(7):1129–36.
- Franchini M and Mannucci PM. Hemophilia A in the third millennium. *Blood Rev* 2013;27:179–84.
- Geraghty S, Dunkley T, Harrington C, et al. Practice patterns in haemophilia A therapy—global progress towards optimal care. *Haemophilia* 2006;12(1):75–81.
- Gringeri A, Lambert T, Street A, et al. Tertiary prophylaxis in adults: is there a rationale? *Haemophilia* 2012;18(5):722–8.
- Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia* 2001;7(4):392–6.
- Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
- Ho S, Gue D, McIntosh K, et al. An objective method for assessing adherence to prophylaxis in adults with severe haemophilia. *Haemophilia* 2013;20:39–43.
- Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22:1717–27.
- Khawaji M, Astermark J, Berntorp E. Lifelong prophylaxis in a large cohort of adult patients with severe haemophilia: a beneficial effect on orthopaedic outcome and quality of life. *Eur J Haematol* 2012;88(4):329–35.
- Kingdon HS and Lundblad RL. An adventure in biotechnology: the development of haemophilia A therapeutics—from whole-blood transfusion to recombinant DNA to gene therapy. *Biotechnol Appl Biochem* 2002;35:141–8.
- Kraft J, Blanchette V, Babyn P, et al. Magnetic resonance imaging and joint outcomes in boys with severe hemophilia A treated with tailored primary prophylaxis in Canada. *J Thromb Haemost* 2012;10(12):2494–502.
- Krishnan S, Vietri J, Furlan R, et al. Adherence to prophylaxis is associated with better outcomes in moderate and severe haemophilia: results of a patient survey. *Haemophilia* 2015;21(1):64–70.
- Lindvall K, Colstrup L, Wollter IM, et al. Compliance with treatment and understanding of own disease in patients with severe and moderate haemophilia. *Haemophilia* 2006;12(1):47–51.

- Ljung R and Gretenkort AN. The current status of prophylactic replacement therapy in children and adults with haemophilia. *BR J Haematol* 2015 Jun;169(6):777–86.
- Llewellyn DD, Miners AH, Lee CA, et al. The illness perceptions and treatment beliefs of individuals with severe haemophilia and their role in adherence to home treatment. *Psychol Health* 2003;18:185–200.
- Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood* 2014;123:317–25.
- Mair FS and May CR. Thinking about the burden of treatment. *BMJ* 2014;349:g6680.
- Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007;357:535–44.
- Mannucci PM and Tuddenham EG. The hemophilias—from royal genes to gene therapy. *N Engl J Med* 2001;344:1773–9.
- Noone D, O'Mahony B, van Dijk JP, et al. A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18-35-year old men with severe haemophilia in six countries. *Haemophilia* 2013;19(1):44–50.
- O'Mahony B, Noone D, Giangrande LF, et al. Haemophilia care in Europe – a survey of 35 countries. *Haemophilia* 2013;19:e239–47.
- Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood* 2015;125(13):2038–44.
- Oldenburg J, Brackmann HH. Prophylaxis in adult patients with severe haemophilia A. *Thromb Res* 2014;134 Suppl 1:S33–7.
- Olivieri M, Kurnik K, Pfluger T, et al. Identification and long-term observation of early joint damage by magnetic resonance imaging in clinically asymptomatic joints in patients with haemophilia A or B despite prophylaxis. *Haemophilia* 2012;18(3):369–74.
- Plug I, Mauser-Bunschoten EP, Brocker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood* 2006;108:52–6.
- Pollak E, Mühlhan H, Von Mackensen S, et al. The Haemo-QoL Index: developing a short measure for health-related quality of life assessment in children and adolescents with haemophilia. *Haemophilia* 2006;12:384–92.
- Rodriguez V, Mancuso ME, Warad D, et al. Central venous access device (CVAD) complications in Haemophilia with inhibitors undergoing immune tolerance induction: Lessons from the international immune tolerance study. *Haemophilia* 2015 Sep;21(5):e369–74.

- Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.
- Santagostino E, Lentz SR, Busk AK, et al. Assessment of the impact of treatment on quality of life of patients with haemophilia A at different ages: insights from two clinical trials on turoctocog alfa. *Haemophilia* 2014;20:527–34.
- Schrijvers LH, Uitslager N, Schuurmans MJ, et al. Barriers and motivators of adherence to prophylactic treatment in haemophilia: a systematic review. *Haemophilia* 2013;19:355–61.
- Schrijvers LH, Kars MC, Beijlvelt-Van Der Zande M, et al. Unravelling adherence to prophylaxis in haemophilia: a patients' perspective." *Haemophilia* 2015;21:612–21.
- Shapiro AD. Long-lasting recombinant factor VIII proteins for hemophilia A. *Am Soc Hematol Educ Program* 2013;2013:37–43.
- Skinner MW. WFH: closing the global gap—achieving optimal care. *Haemophilia* 2012;18 Suppl 4:1–12.
- Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia* 2013;19(1):e1–47.
- Stasyshyn O, Antunes S, Mamonov V, et al. Prophylaxis with anti-inhibitor coagulant complex improves health-related quality of life in haemophilia patients with inhibitors: results from FEIBA NF Prophylaxis Study. *Haemophilia* 2014;20:644–50.
- Teal S, Brohan E, Hettema Y, et al. Development and psychometric evaluation of a novel tool for assessing patient perception and preference for haemophilia treatment (HaemoPREF). *Haemophilia* 2014;20(5):666–73.
- Valentino LA, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost* 2012;10:359–67.
- Vepsäläinen K, Lassila R, Arola M, et al. Complications associated with central venous access device in children with haemophilia: a nationwide multicentre study in Finland. *Haemophilia*. 2015 Nov;21(6):747–53.
- von Mackensen S and Bullinger M. Development and testing of an instrument to assess the Quality of Life of Children with Haemophilia in Europe (Haemo-QoL). *Haemophilia* 2004;10(Suppl. 1):17–25.
- von Mackensen S and Gringeri A. Health related quality of life in adult patients with haemophilia – assessment with a new disease-specific questionnaire [abstract]. *J Thromb Haemost* 2005;3:P0813.

von Mackensen S and Gringeri A. Quality of life in hemophilia, Chapter 112. In: Preedy VR, Watson RR eds. Handbook of Disease Burdens and Quality of Life. Heidelberg: Springer, 2010:1896–920.

World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. Geneva: World Health Organization; 2003.

World Federation of Hemophilia. Annual Global Survey Data 2013. Accessed April 22, 2015, from:  
[http://www1.wfh.org/GlobalSurvey/Public\\_AGS/AGS\\_Patients\\_Severity\\_EN.aspx](http://www1.wfh.org/GlobalSurvey/Public_AGS/AGS_Patients_Severity_EN.aspx).

## Appendix 1 Schedule of Assessments

PK RUN-IN COHORT															
Week  Day <sup>b</sup>	Screening		Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination <sup>a</sup>	Safety F/U Visit
	—	—	1	2	3	4	5	9	13	17	21	25			
	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169			
Informed consent <sup>c</sup>	x														
Inclusion/exclusion criteria	x														
Demographics and medical history <sup>d</sup>	x														
Physical examination including height and weight <sup>e</sup>	x		x <sup>f</sup>		x <sup>f</sup>		x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	Q12W <sup>f</sup>	x <sup>f</sup>	x
Vital signs <sup>g</sup>	x		x	x		x	x	x	x	x	x	x	Q12W	x	x
Concomitant medications <sup>h</sup>			x		x		x	x	x	x	x	x	Q12W	x	x
Adverse events <sup>i</sup>			Ongoing												
12-lead ECG <sup>j</sup>	x						x <sup>k</sup>					x	x <sup>l</sup>	x	
Hematology <sup>m</sup>		x	x	x	x		x	x	x	x	x	x	Q12W	x	x
Blood chemistry <sup>n</sup>		x	x	x	x		x	x	x	x	x	x	Q12W	x	x
Pregnancy test <sup>o</sup>	x	x	x	x	x		x	x	x	x	x	x	Q12W	x	x
Emicizumab administration <sup>p</sup>			x				x	x	x	x	x	x	Q4W		
PK, PD, and ADA	See <a href="#">Appendix 2</a>														



## Appendix 1 Schedule of Assessments (cont.)

PK RUN-IN COHORT															
Week  															

ADA = anti-drug antibody; eCRF = electronic Case Report Form; EQ-5D-5L = European Quality of Life 5-Dimension, 5-Level questionnaire; F/U = follow-up; HRQoL = health-related quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; Q4W = every 4 weeks; Q12W = every 12 weeks.

- <sup>a</sup> Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.
- <sup>b</sup> In order to characterize pharmacokinetics, it is mandatory *for* assessments *to* be performed on the exact visit day until Week 25; no deviation from visit day is acceptable until Week 25, deviations of  $\pm 2$  days are acceptable thereafter *until safety follow-up visit*. *Safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab, deviation of +7 days is acceptable. The safety follow-up visit will not be performed for patients who transfer to an extension study or to commercial emicizumab.*
- <sup>c</sup> Obtain written informed consent (or patient written assent and parent written informed consent if patient is an adolescent) before performing any study related procedures. If patient fulfils the inclusion criteria, the patient should be enrolled in the study on the same day when the first dose of emicizumab is administered (Day 1).
- <sup>d</sup> Collected from patient's medical record and documented in the eCRF.
- <sup>e</sup> Height assessment at Day 1 only for adults and weight assessments Q4W for all patients.
- <sup>f</sup> Height assessments for adolescents at Day 1 and ideally at all drug administration and PK sampling visits when the patients will be at the investigational site but at least every 12 weeks (repeated assessments).
- <sup>g</sup> Body temperature (oral, tympanic, *or axillary*), blood pressure, pulse rate, respiratory rate.

## Appendix 1

### Schedule of Assessments (cont.)

- 
- <sup>h</sup> Concomitant medication (e.g., extra pain medication to treat bleeds) will be recorded at the time of the visits, excluding treatments for bleeds, which will be collected in the bleeding questionnaire.
- <sup>i</sup> Adverse events are collected on an ongoing basis throughout the study. Injection-site reactions will be collected on a separate form from the adverse event form. After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.
- <sup>j</sup> If screening ECG is abnormal, repeat at Week 1. ECGs will also be performed: once during Weeks 4–8 after starting emicizumab or dose escalation (up-titration); once 24 weeks after starting emicizumab or dose escalation (up-titration); and at study completion/early termination.
- <sup>k</sup> Once during Weeks 4–8 after starting emicizumab.
- <sup>l</sup> For any dose increase (i.e., 3 mg/kg QW), an ECG should be obtained after 4–8 weeks *and 24 weeks after dose up-titration, as well as at study completion/early termination.*
- <sup>m</sup> Predose (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width), performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. *If patients undergo up-titration of their dose after ≥ 24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration.*
- <sup>n</sup> Predose (sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), performed locally. Laboratory assessments completed at the screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. *If patients undergo up-titration of their dose after ≥ 24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration.*
- <sup>o</sup> Female patients with childbearing potential will be required to have a negative serum pregnancy test result at Screening and up to 7 days prior to enrollment (Day – 7 to Day – 1). If applicable, during the study, urine pregnancy tests will be performed at the scheduled visits.
- <sup>p</sup> 6 mg/kg Q4W emicizumab.
- <sup>q</sup> Bleed information (start date and time, reason, type, location, and associated symptoms of each bleed) and medication for bleeds (breakthrough bleeds) should be reported by the patient via an electronic handheld device when a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days). If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient until the safety follow-up visit (24 weeks after last study drug administration). *Emicizumab doses should be recorded by the patient in the bleed/medication questionnaire starting from Day 1.*
- <sup>r</sup> Investigator review of bleed information.
- <sup>s</sup> Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents. If applicable, laboratory results should be recorded on the *Following Treatments with Bypassing Agents* eCRF.

## Appendix 1 Schedule of Assessments (cont.)

Expansion Cohort															
	Screening		Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination <sup>a</sup>	Safety Follow- Up Visit
	Week		1	2	3	4	5	9	13	17	21	25			
	Day <sup>b</sup>	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141	169		
Informed consent <sup>c</sup>	x														
Inclusion/exclusion criteria	x														
Demographics and medical history <sup>d</sup>	x														
Physical examination including height and weight <sup>e</sup>	x		x <sup>f</sup>		x <sup>f</sup>		x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	x <sup>f</sup>	Q12W <sup>f</sup>	x <sup>f</sup>	x
Vital signs <sup>g</sup>	x		x	x		x	x	x	x	x	x	x	Q12W	x	x
Concomitant medications <sup>h</sup>			x		x		x	x	x	x	x	x	Q12W	x	x
Adverse events <sup>i</sup>			Ongoing												
12-lead ECG <sup>j</sup>	x						x <sup>k</sup>					x	x <sup>l</sup>	x	
Hematology <sup>m</sup>		x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Blood chemistry <sup>n</sup>		x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Pregnancy test <sup>o</sup>	x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x

## Appendix 1 Schedule of Assessments (cont.)

Expansion Cohort															
Week	Screening		Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination <sup>a</sup>	Safety Follow-Up Visit
	—	—	1	2	3	4	5	9	13	17	21	25			
	Day <sup>b</sup>	–28 to –1	–7 to –1	1	8	15	22	29	57	85	113	141			
PRO (HRQoL) <sup>p</sup>			x						x			x	Q12W	x	
Days missed from school/work <sup>q</sup>			x						x			x	Q12W	x	
PRO (Preference)										x <sup>r</sup>					
Health status (EQ-5D-5L) <sup>s</sup>			x						x			x	Q12W	x	
Emicizumab administration <sup>t</sup>			x	x	x	x	x	x	x	x	x	x	Q4W		
PK, PD, ADA	See <a href="#">Appendix 2</a>														
Bleed/medication questionnaire <sup>u</sup>			Weekly and on days of bleed										x	x	
Bleed/medication review <sup>v</sup>			x				x	x	x	x	x	x	Q4W	x	x
Following treatments with bypassing agents <sup>w</sup>			Monitoring for thromboembolic events and thrombotic microangiopathy <sup>w</sup>												

## Appendix 1

### Schedule of Assessments (cont.)

ADA = anti-drug antibody; eCRF = electronic Case Report Form; EQ-5D-5L = European Quality of Life 5-Dimension, 5-Level questionnaire; ET = early termination; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = factor XIII; HRQoL = health-related quality of life; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; Q4W = every 4 weeks; Q12W = every 12 weeks.

- <sup>a</sup> Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.
- <sup>b</sup> Assessments can deviate from planned schedule by  $\pm 2$  days until safety follow-up visit. Safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab; deviation of  $\pm 7$  days is acceptable. Safety follow-up visit will not be performed for patients who transfer to an extension study or to commercial emicizumab.
- <sup>c</sup> Obtain written informed consent (or patient written assent and legal representative written informed consent if patient is an adolescent) before performing any study related procedures. If patient fulfils the inclusion criteria, the patient should be enrolled in the study on the same day when the first dose of emicizumab is administered (Day 1).
- <sup>d</sup> Collected from patient's medical record and documented in the eCRF.
- <sup>e</sup> Height assessment at Day 1 only for adults and weight assessments Q4W for all patients.
- <sup>f</sup> Height assessments for adolescents at Day 1 and ideally at all drug administration and PK sampling visits that the patients will be at the investigational site, but at least every 12 weeks (repeated assessments).
- <sup>g</sup> Body temperature (oral, tympanic, or axillary), blood pressure, pulse rate, respiratory rate.
- <sup>h</sup> Concomitant medication (e.g., extra pain medication to treat bleeds) will be recorded at the time of the visits, excluding treatments for bleeds, which will be collected in the bleeding questionnaire starting from Day 1. FVIII taken in the week prior to starting emicizumab (week prior to Day 1) will also be collected on the Concomitant Medication eCRF page for patients without inhibitors to FVIII who will continue their prior FVIII prophylaxis during the first week of the study.
- <sup>i</sup> Adverse events are collected on an ongoing basis throughout the study. Injection-site reactions will be collected on a separate form from the adverse event form. After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.
- <sup>j</sup> If screening ECG is abnormal, repeat at Week 1. ECGs will also be performed: once during Weeks 4–8 after starting emicizumab or dose escalation (up-titration); once 24 weeks after starting emicizumab or dose escalation (up-titration); and at study completion/early termination.
- <sup>k</sup> Once during Weeks 4–8 after starting emicizumab.
- <sup>l</sup> For any dose increase (i.e., 3 mg/kg QW), an ECG should be obtained after 4–8 weeks and 24 weeks after dose up-titration, as well as at study completion/early termination.
- <sup>m</sup> Predose: (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width), performed locally. Laboratory assessments completed at the Screening visit do not have to be repeated at Week 1 if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. If patients undergo up-titration of their dose after  $\geq 24$  weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration.

## Appendix 1

### Schedule of Assessments (cont.)

---

- <sup>n</sup> Predose (e.g., sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), performed locally. Laboratory assessments completed at the Screening visit do not have to be repeated at Week 1, if the period between Screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. *If patients undergo up-titration of their dose after ≥ 24 weeks on emicizumab, an additional blood draw for safety laboratory assessments should be performed within the first 4 weeks after up-titration.*
- <sup>o</sup> Female patients with childbearing potential will be required to have a negative serum pregnancy test result at Screening and up to 7 days prior to enrollment (Day – 7 to Day – 1). If applicable, during the study, urine pregnancy tests will be performed at the scheduled visits.
- <sup>p</sup> Day 1 assessment predose (= baseline), followed by assessments at Week 13 predose and Week 25 predose by Haem-A-QoL (age > 18 years) and Haemo-QoL-Short Form (ages 12–17 years).
- <sup>q</sup> Day 1 assessment predose (= baseline), followed by assessments at Week 13 predose and Week 25 predose.
- <sup>r</sup> Predose.
- <sup>s</sup> Day 1 assessment predose (= baseline), followed by assessments at Week 13 predose and Week 25 predose by EQ-5D-5L questionnaire.
- <sup>t</sup> 3 mg/kg QW emicizumab loading dose *for 4 weeks*, followed by 6 mg/kg Q4W emicizumab maintenance dose.
- <sup>u</sup> Bleed information (start date and time, reason, type, location, and associated symptoms of each bleed) and medication for bleeds (breakthrough bleeds) should be reported by the patient via an electronic, handheld device when a bleed occurs or at least on a weekly basis (retrospective reporting for last 7 days). If the patient discontinues study treatment, bleed and bleed medication data should be provided by the patient until the safety follow-up visit (24 weeks after last study drug administration). *Emicizumab doses should be recorded by the patient in the bleed/medication questionnaire starting from Day 1.*
- <sup>v</sup> Investigator review of bleed information.
- <sup>w</sup> Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents. In the case that such local laboratory tests are performed, laboratory results should be recorded on the *Following Treatments with Bypassing Agents* eCRF.

## Appendix 2

### Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

PK RUN-IN																												
	Screen -ing	Treatment Period																				From Week 25 to Study Com- pletion	Study Com- pletion or ET <sup>a</sup>	Safety F/U visit				
Week		1			2		3		4		5	6	7	8	9	10 to 12 <sup>b</sup>	13	14 to 16 <sup>b</sup>	17	18 to 20 <sup>b</sup>	21	22	23	24	25			
Day	-28 to -1 days	1	3	5	8	11	15	18	22	25	29	36	43	50	57		85		113		141	148	155	162	169			
Emicizumab PK <sup>b</sup>		x	x <sup>c,d</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Q12W	x	x	
Emicizumab ADA <sup>d</sup>		x									x				x		x		x		x				x	Q12W	x	x
Emicizumab biomarker set 1 <sup>e</sup>		x									x		x		x	x <sup>f</sup>	x	x <sup>f</sup>	x	x <sup>f</sup>	x		x		x	Q12W	x	x
Emicizumab biomarker set 2 <sup>g</sup>			x <sup>c</sup>	x	x	x	x	x	x	x																		
Anti-FVIII antibodies <sup>h, i</sup>	x	x													x				x						x	Q12W	x	x
Following treatments with bypassing agents		Monitoring for thromboembolic events and thrombotic microangiopathy <sup>j</sup>																										

ADA = anti-drug antibody; ET = early termination; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = Factor XIII; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; Q12W = every 12 weeks.

## Appendix 2

### Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

---

Note: Blood samples should always be drawn predose (if taken on days of emicizumab administration); consult the Sample Handling Manual for details. PD biomarker tests will include, but are not limited to those listed here. In order to characterize pharmacokinetics, it is mandatory that assessments are being performed on the exact visit day until Week 25; no deviation from visit day is acceptable until Week 25. Deviations from the schedule of assessments of  $\pm 2$  days are acceptable after Week 25.

- <sup>a</sup> Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.
- <sup>b</sup> During the first 8 weeks, PK sampling will occur at the following timepoints: Week 1 (predose Day 1; 8 hours post-injection on Day 1; then Day 3, Day 5), Week 2 (Day 8, Day 11), Week 3 (Day 15, Day 18), Week 4 (Day 22), Week 5 (Day 29 predose), Week 6 (Day 36), Week 7 (Day 43), and Week 8 (Day 50). A reduced PK sampling schedule will follow to characterize repeated Q4W SC administration from Week 9 to Week 25. From Week 9 to Week 21, patient will have PK blood samples taken at Week 9 (Day 57), Week 13 (Day 85), Week 17 (Day 113), and Week 21 (Day 141). From Week 9 to Week 21, additionally the patient will return once between two emicizumab administrations for a blood sample to be drawn for PK analysis; patients can decide whether this sampling will be 1, 2, or 3 weeks after the latest injection. An individual patient may choose each of the specific intervals (1, 2, or 3 weeks after to the latest injection) at least once. After the sixth injection at Week 21, PK sampling frequency will be increased to characterize steady-state pharmacokinetics, with samples collected at Week 22 (Day 148), Week 23 (Day 155), and Week 24 (Day 162). Another sample will be taken at Week 25 (Day 169) followed by PK assessments every 12 weeks until study completion.
- <sup>c</sup> 8 hours postdose on Day 1.
- <sup>d</sup> Emicizumab ADA blood samples may also be drawn to if hypersensitivity event occur or on an unscheduled basis (at the clinical judgment of the investigator) at any time.
- <sup>e</sup> Set 1=Standard aPTT, modified aPTT, PT, FVIII activity, thrombin generation, FIX antigen, FX antigen, FVIII antigen (baseline only), D-dimer, prothrombin fragment 1.2, vWF antigen (timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit), fibrinogen (timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit), and FXIII activity (baseline only).
- <sup>f</sup> PD assessments occurring once between two Q4W emicizumab administrations to be done on the same day the PK sample is taken (see footnote above).
- <sup>g</sup> Set 2=FVIII activity, D dimer, prothrombin fragment 1.2, standard aPTT, modified aPTT, and PT.
- <sup>h</sup> A sample for inhibitor testing (anti-FVIII antibodies) must be obtained during screening, within 4 weeks prior to enrollment (i.e., before initiation of Week 1, Day 1 assessments). The results must be available before enrollment, and local testing will not replace the central laboratory inhibitor testing performed at Week 1.
- <sup>i</sup> Starting at Week 1, this and all subsequent anti-FVIII antibodies will be measured at a central laboratory. Anti-FVIII antibodies will be tested by a central laboratory at Week 1, Week 25, every 12 weeks thereafter, at the completion visit, and safety follow-up visit for all patients. Testing at Week 9 (Day 57) and Week 17 (Day 113) for non-inhibitor patients only.



## Appendix 2

### Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

---

- <sup>j</sup> Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents. In the case that such local laboratory tests are performed, laboratory results should be recorded on the *Following Treatments with Bypassing Agents* eCRF.

## Appendix 2

### Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

EXPANSION COHORT														
	Screen -ing	Treatment Period										From Week 25 to Study Completion	Study Completion or Early Termination <sup>a</sup>	Safety F/U Visit
Week		1	2	3	4	5	9	13	17	21	25			
Day	-28 to -1 days	1	8	15	22	29	57	85	113	141	169			
Emicizumab PK		x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Emicizumab ADA <sup>b</sup>		x				x	x	x	x	x	x	Q12W	x	x
Emicizumab biomarker set 3(EDTA) <sup>c</sup>			x	x	x						x	Q12W		
Emicizumab biomarker set 1 <sup>d</sup>		x	x	x	x	x	x	x	x	x	x	Q12W	x	x
Anti-FVIII antibodies <sup>e, f</sup>	x	x					x		x		x	Q12W	x	x
Following treatments with bypassing agents		Monitoring for thromboembolic events and thrombotic microangiopathy. <sup>g</sup>												

## Appendix 2

### Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

---

ADA=anti-drug antibody; F/U=follow-up; FIX=factor IX; FVIII=factor VIII; FX=factor X; FXIII=Factor XIII; PK=pharmacokinetic; Q12W=every 12 weeks.

Note: Blood samples should always be drawn predose (if taken on days of emicizumab administration); consult the Sample Handling Manual for details. PD biomarker tests will include but are not limited to those listed here. In order to characterize pharmacokinetics, it is mandatory that assessments are being performed within  $\pm 2$  days of the scheduled visits.

- <sup>a</sup> Study completion visit when either the patient completed 24 weeks' study duration and transferred to an emicizumab extension study OR patient has completed the 24-week safety follow-up visit after emicizumab discontinuation OR patient is lost to follow-up. If study completion occurs after 24 weeks in the study, the completion assessments displayed in the schedule of assessments are similar with the Week 25 visit.
- <sup>b</sup> Emicizumab ADA blood samples may also be drawn if hypersensitivity event occurs or on an unscheduled basis (at the clinical judgment of the investigator) at any time.
- <sup>c</sup> Set 3=Exploratory biomarker assay of emicizumab concentration that requires EDTA rather than citrate plasma.
- <sup>d</sup> Set 1=Standard aPTT, modified aPTT, PT, FVIII activity, thrombin generation, FIX antigen, FX antigen, D-dimer, prothrombin fragment 1.2 vWF antigen (timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit), and fibrinogen (timepoints of Week 1 Day 1, Week 13, Week 25, study completion or ET, safety follow-up visit).
- <sup>e</sup> A sample inhibitor testing (anti-FVIII antibodies) must be obtained within 8 weeks prior to enrollment, (i.e., before initiation of Week 1, Day 1 assessments). The results must be available before enrollment, and local testing will not replace the central laboratory inhibitor testing performed at Week 1.
- <sup>f</sup> Starting at Week 1, this and all subsequent anti-FVIII antibodies will be measured at a central laboratory. Anti-FVIII antibodies will be tested by a central laboratory at Week 1, Week 25, every 12 weeks thereafter, at the completion visit, and safety follow-up visit for all patients. Testing at Week 9 (Day 57) and Week 17 (Day 113) is for non-inhibitor patients only.
- <sup>g</sup> Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be sent to the local reference laboratory, if available. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents. In the case that such local laboratory tests are performed, laboratory results should be recorded on the *Following Treatments with Bypassing Agents* eCRF.

### Appendix 3

## WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

<b>HEMATOLOGY</b>				
Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	< 6.5 g/dL
Absolute neutrophil count	1000–1500/mm <sup>3</sup>	750–999/mm <sup>3</sup>	500–749/mm <sup>3</sup>	< 500/mm <sup>3</sup>
Platelets	75000–99999/mm <sup>3</sup>	50000–74999/mm <sup>3</sup>	20000–49999/mm <sup>3</sup>	< 20000/mm <sup>3</sup>
Prothrombin time (PT)	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	> 3 × ULN
Activated partial thromboplastin (APPT)	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	> 3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25–0.49 × LLN	< 0.25 × LLN
Fibrin split product	20–40 mcg/mL	41–50 mcg/mL	51–60 mcg/mL	> 60 mcg/mL
Methemoglobin	5–9.9%	10.0–14.9%	15.0–19.9%	> 20 %
<b>LIVER ENZYMES</b>				
AST (SGOT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
GGT	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Alkaline phosphatase	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN

### Appendix 3

## WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

LIVER ENZYMES continued				
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	> 5.0 × ULN
CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required.	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	< 30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	< 6.1 mg/dL or life-threatening arrhythmia or tetany

### Appendix 3

## WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

<b>CHEMISTRIES continued</b>				
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	< 0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	> 5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	> 6 × ULN or required dialysis
<b>URINALYSIS</b>				
Proteinuria	1 + or < 0.3% or < 3g/L or 200 mg–1 g loss/day	2–3 + or 0.3–1.0% or 3–10 g/L 1–2 g loss/day	4 + or > 1.0% or > 10 g/L 2–3.5 g loss/day	nephrotic syndrome or > 3.5 g loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion

### Appendix 3

## WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

<b>CARDIAC DYSFUNCTION</b>				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
Hypertension	transient increase. > 20 mmHg; no Rx required	recurrent, chronic, increase > 20 mmHg, Rx required	requires acute Rx; no hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1–2 units transfused	massive blood loss; > 3 units transfused
<b>RESPIRATORY</b>				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 70%–79% FEV <sub>1</sub> (or peak flow)	requires Rx normalizes with bronchodilator; FEV <sub>1</sub> 50%–69% (or peak Flow)	no normalization with bronchodilator; FEV <sub>1</sub> 25%–49% (or peak flow retractions)	cyanosis: FEV <sub>1</sub> < 25% (or peak flow) or intubated

### Appendix 3

## WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

<b>GASTROINTESTINAL</b>				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3–4 loose stools/day	5–7 loose stools/day	orthostatic hypotension or > 7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
<b>NEURO AND NEUROMUSCULAR</b>				
Neuro-cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization



### Appendix 3

## WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

NEURO AND NEUROMUSCULAR continued				
Neuro control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle strength	subjective weakness no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7–38.5°C or 99.9–101.3°F	38.6–39.5°C or 101.4–103.1°F	39.6–40.5°C or 103.2–104.9°F	> 40.5°C or > 104.9°F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25–50%	normal activity decreased > 50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis

### Appendix 3

## WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

OTHER PARAMETERS continued				
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration ≥ 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens- Johnson or necrosis requiring surgery

## **Appendix 4**

### **Clinical Criteria for Diagnosing Anaphylaxis**

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.<sup>1</sup> Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

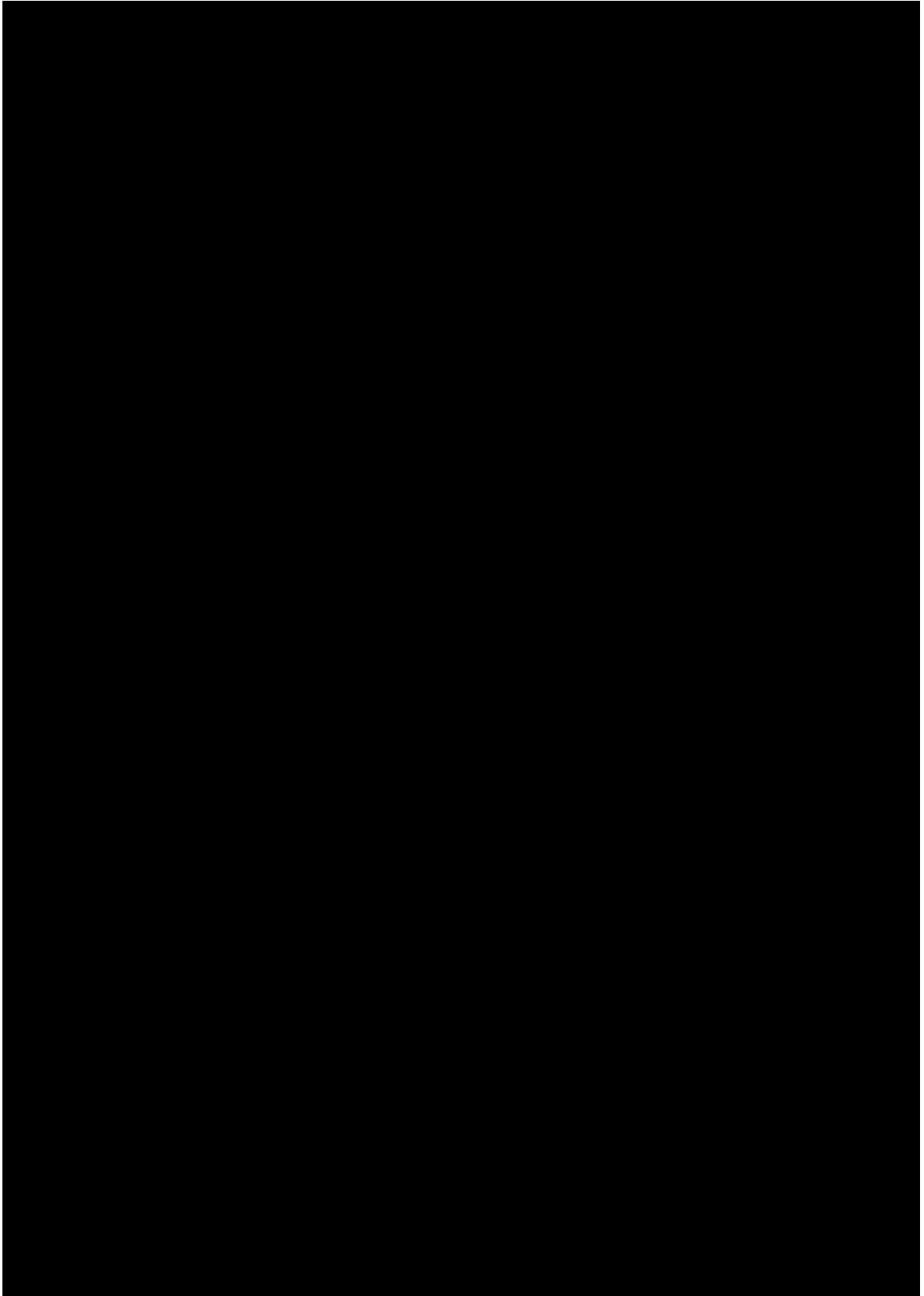
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula)  
AND AT LEAST ONE OF THE FOLLOWING:
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
  - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
  - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure<sup>2</sup>
  - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

---

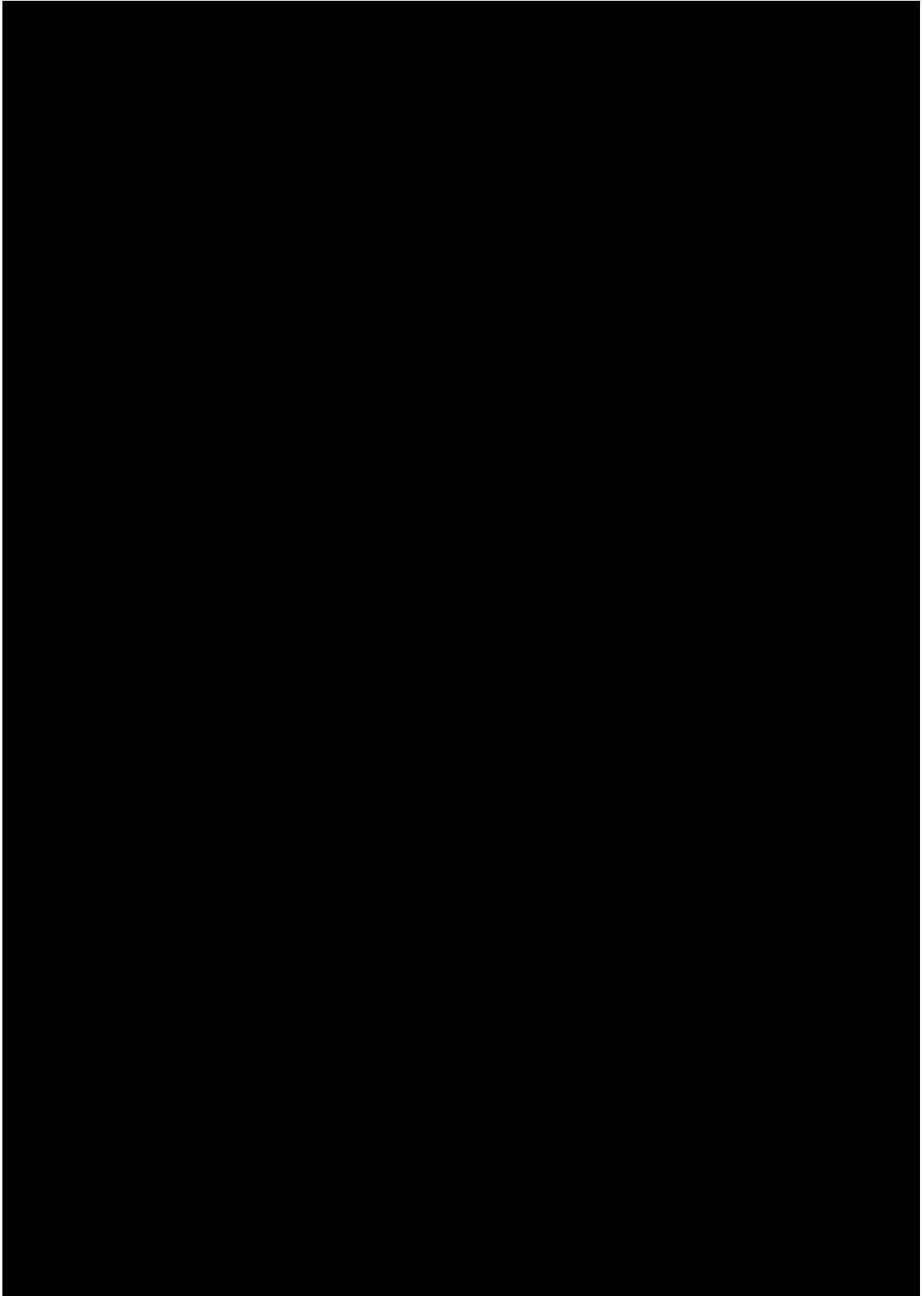
<sup>1</sup> Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.

<sup>2</sup> Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

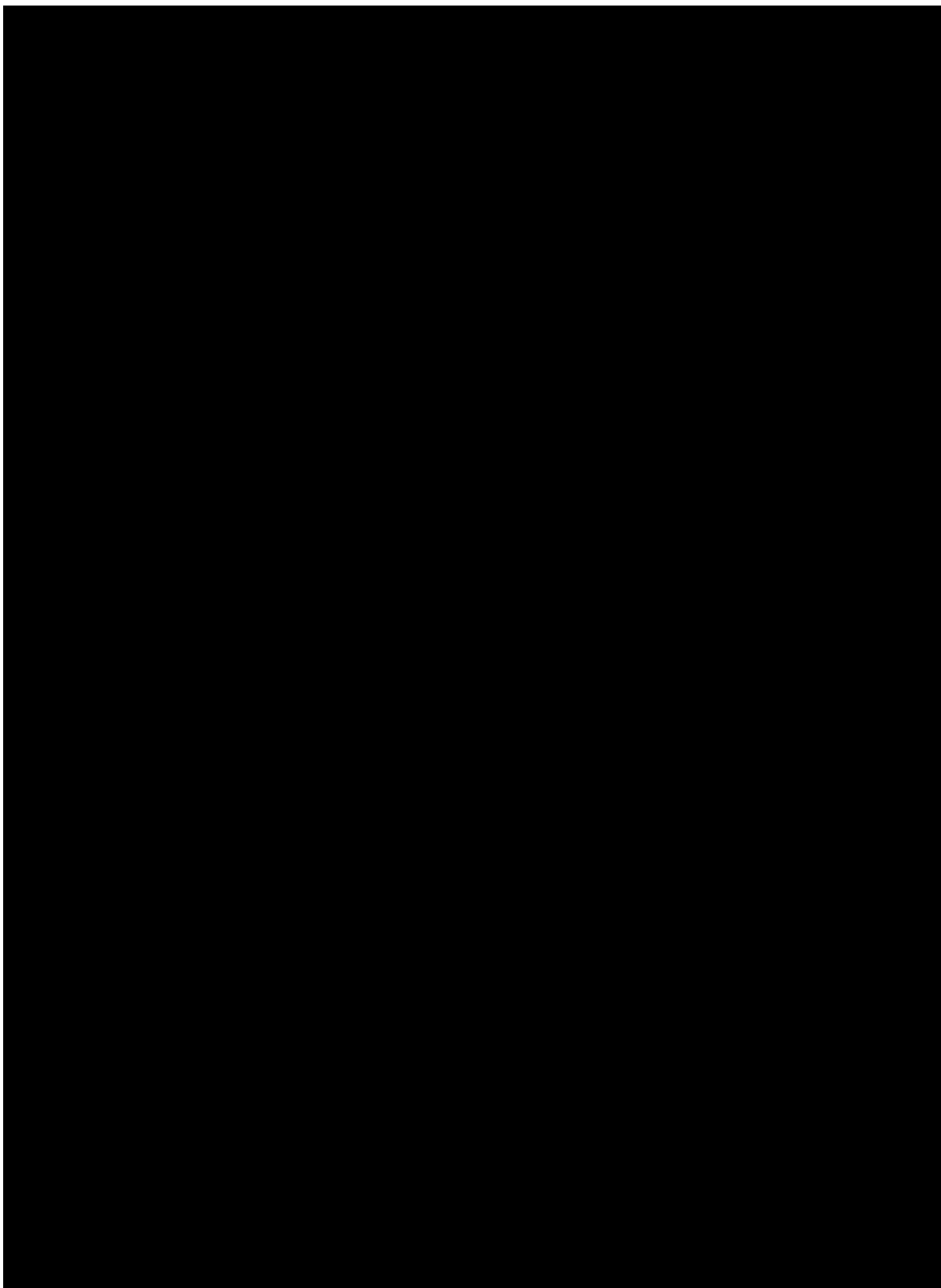
**Appendix 5**  
**Haemo-QoL-SF (United States/English)**



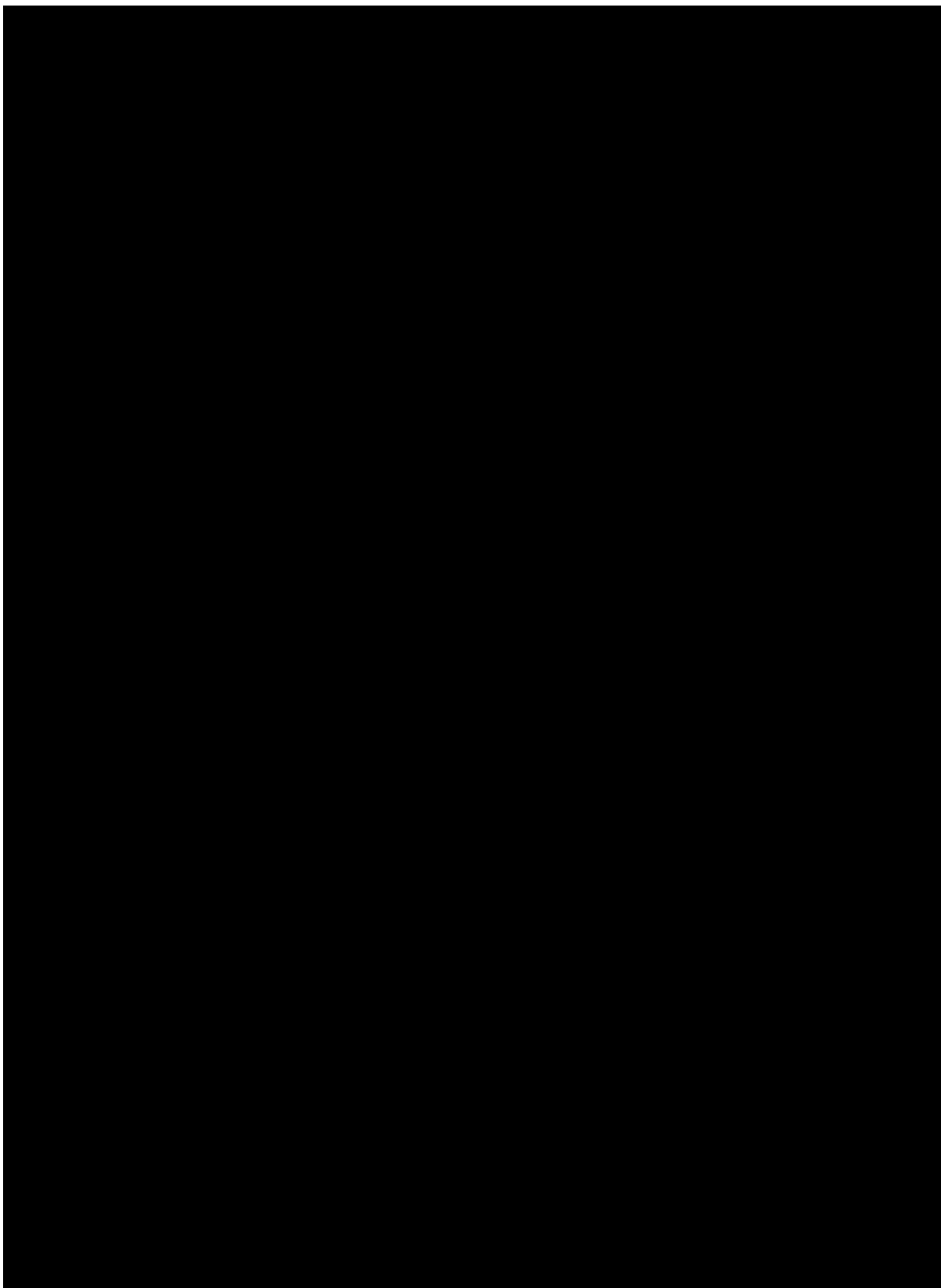
**Appendix 5**  
**Haemo-QoL-SF (United States/English) (cont.)**



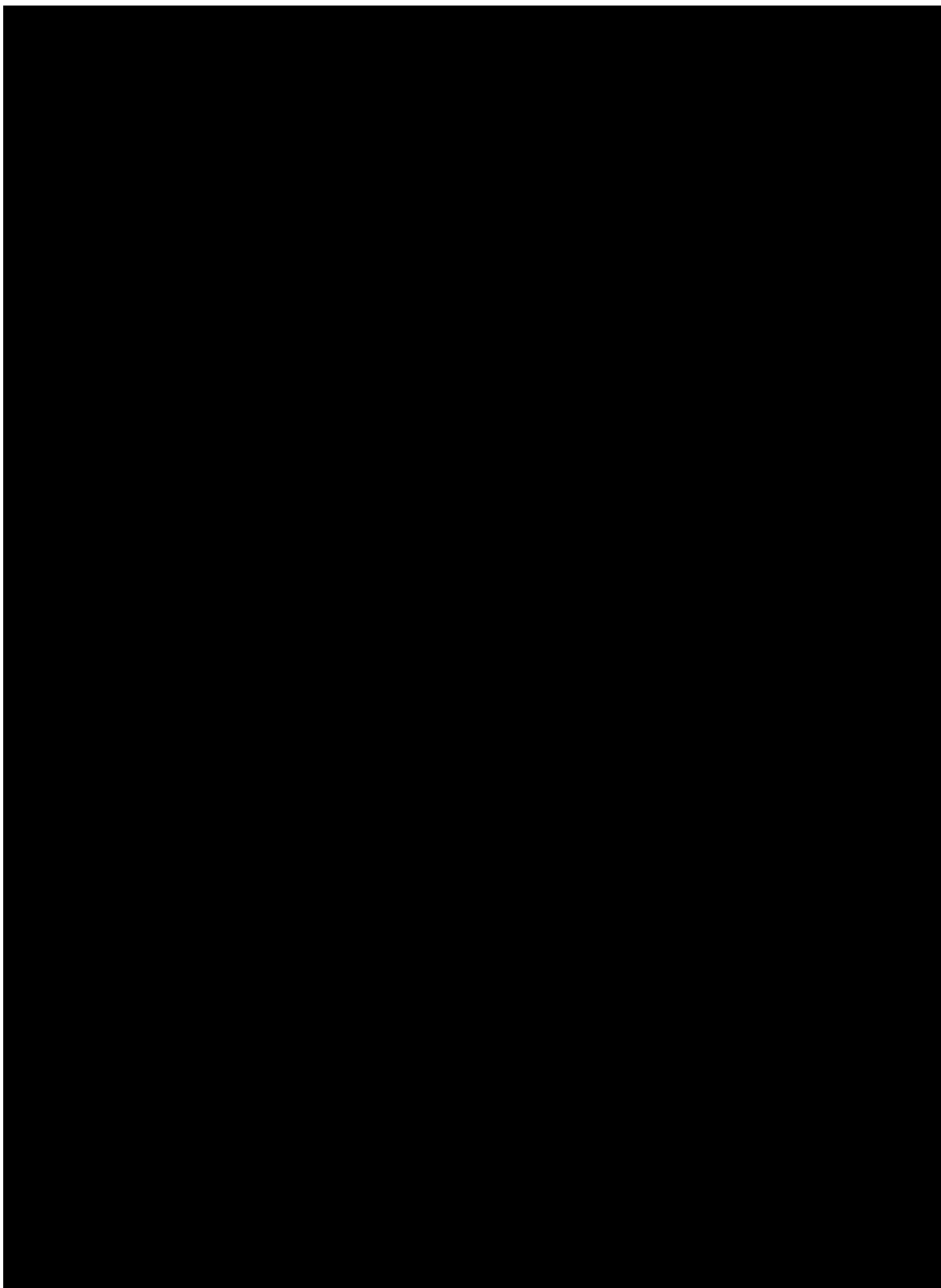
**Appendix 6**  
**Haem-A-QoL (United States/English)**



**Appendix 6**  
**Haem-A-QoL (United States/English) (cont.)**

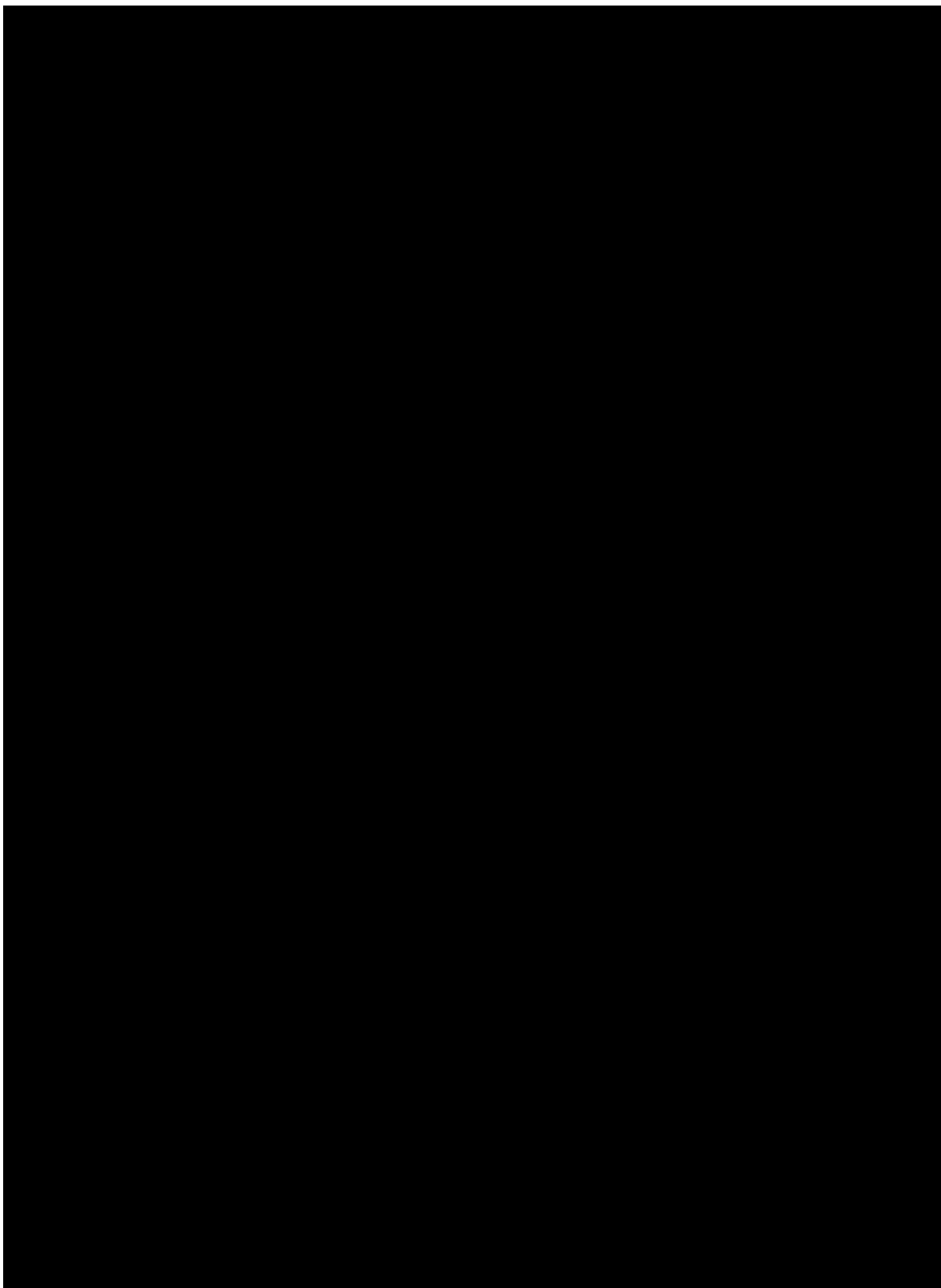


**Appendix 6**  
**Haem-A-QoL (United States/English) (cont.)**

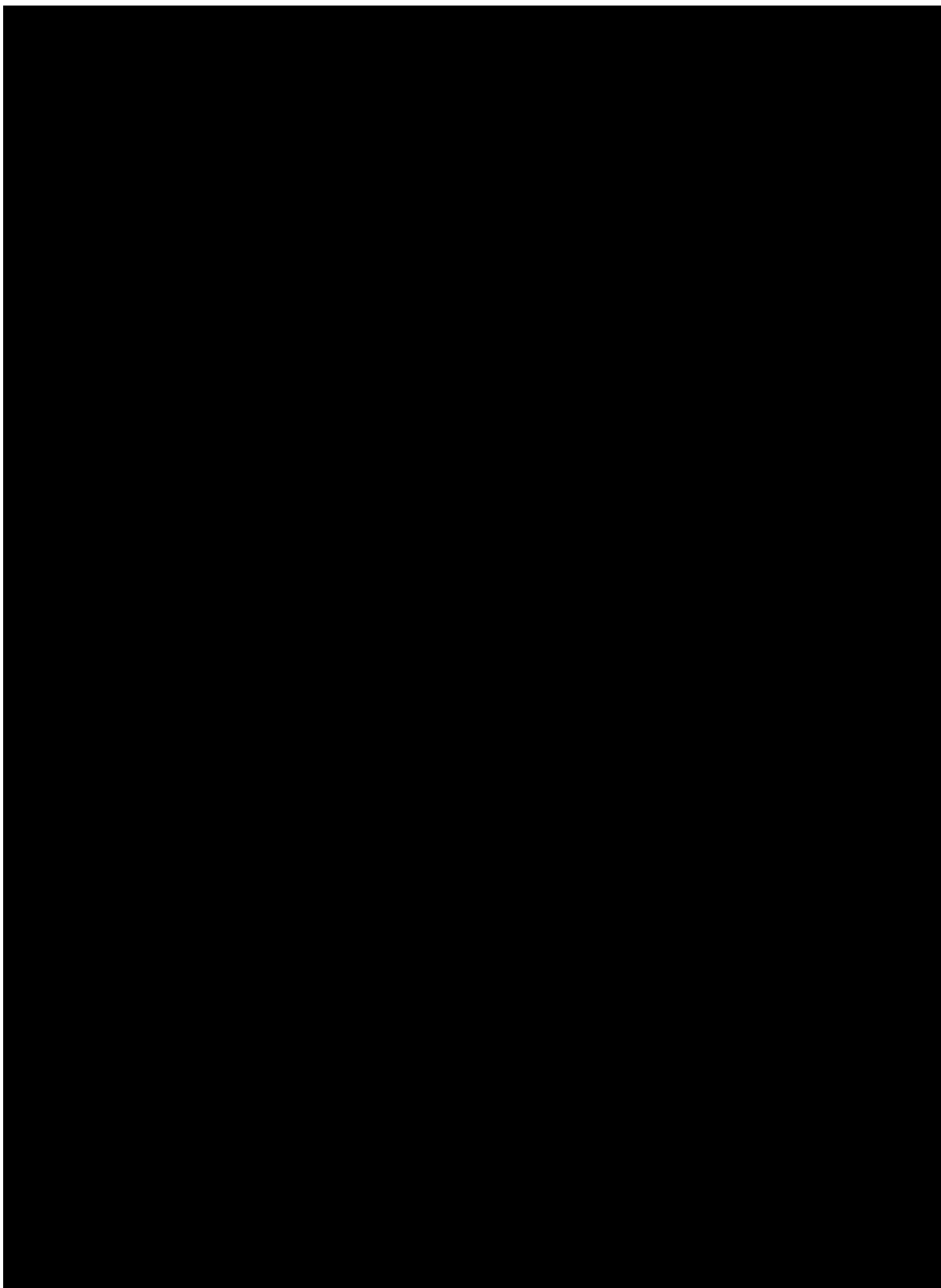




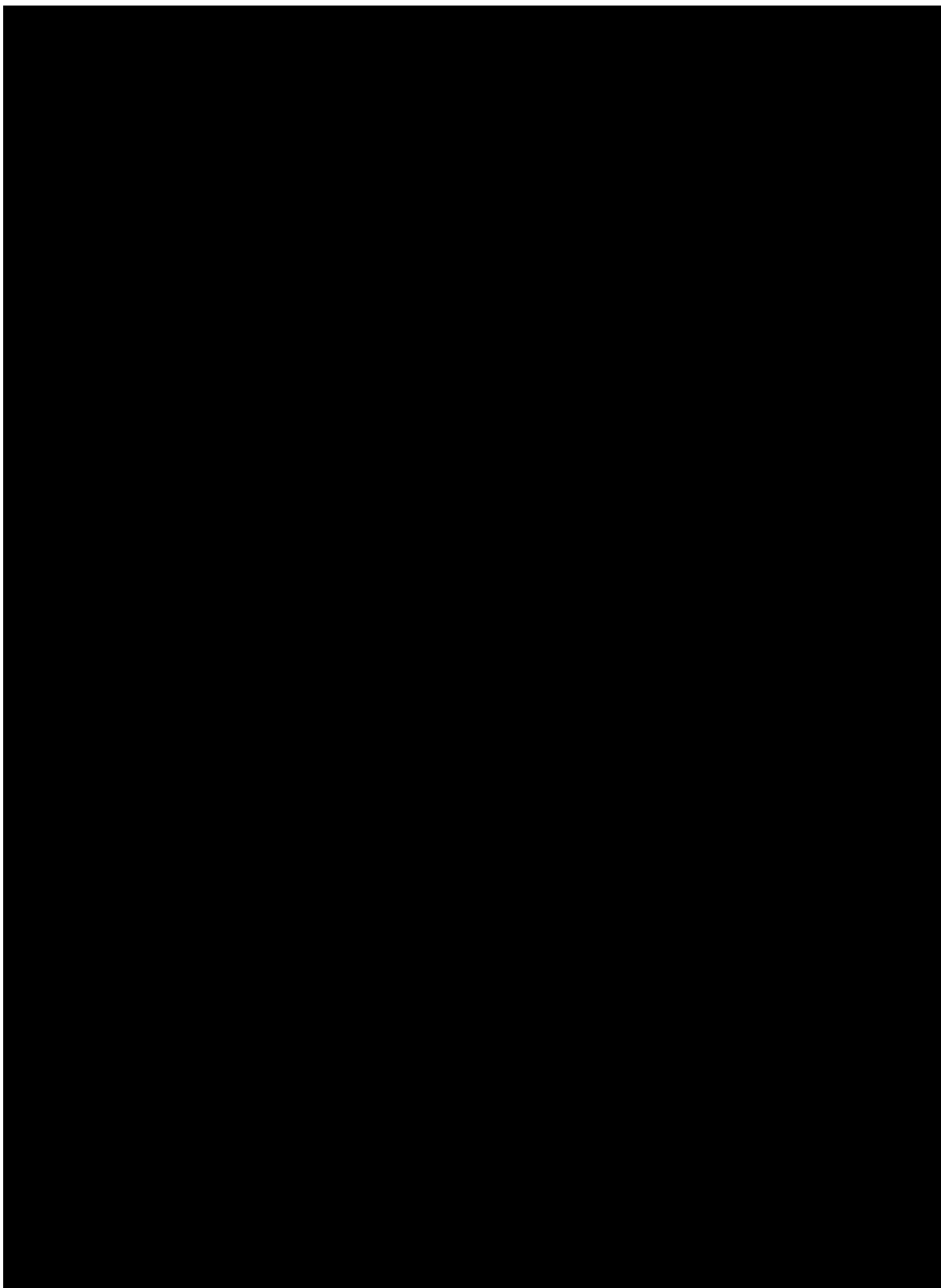
**Appendix 6**  
**Haem-A-QoL (United States/English) (cont.)**



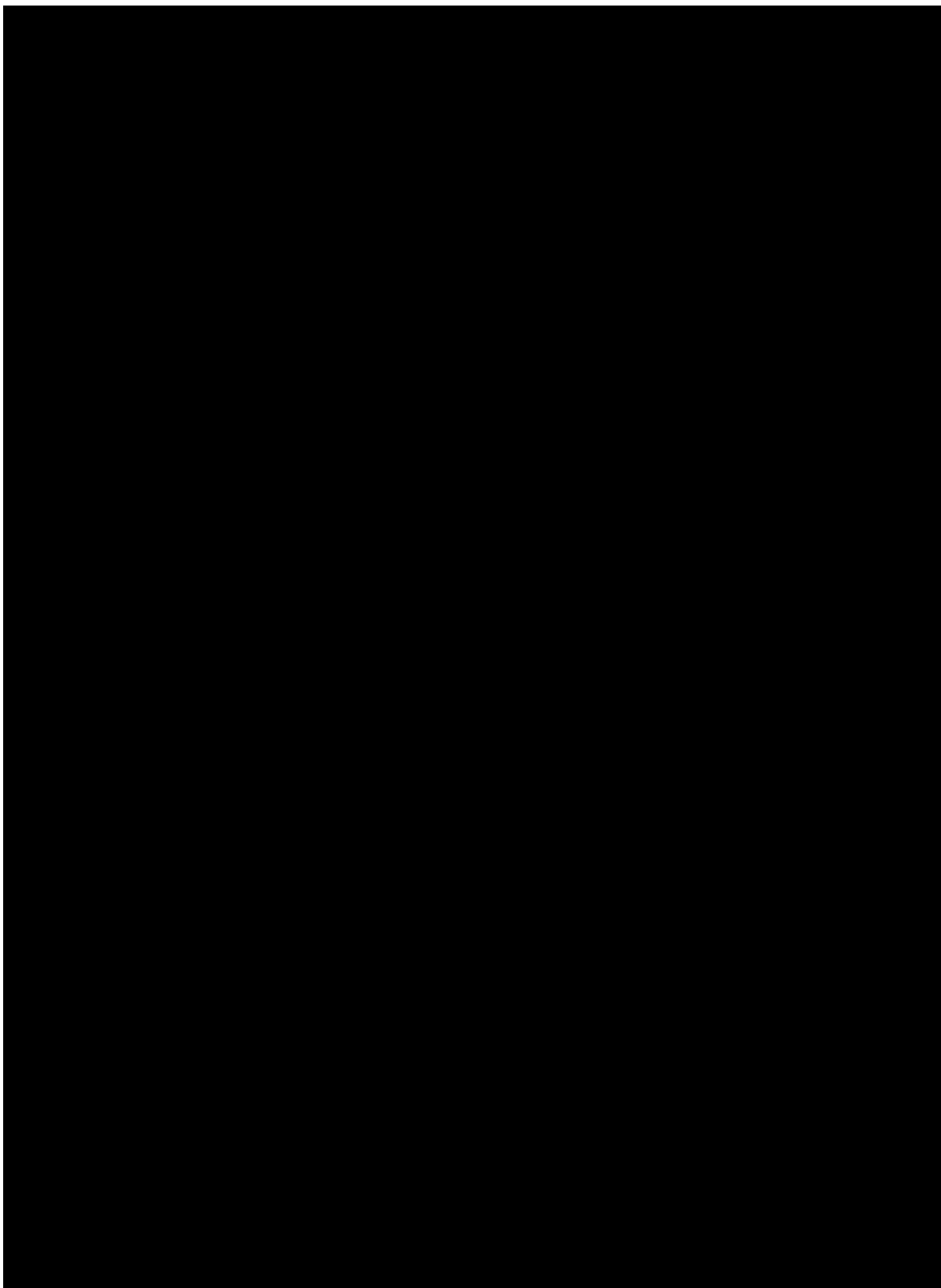
**Appendix 6**  
**Haem-A-QoL (United States/English) (cont.)**



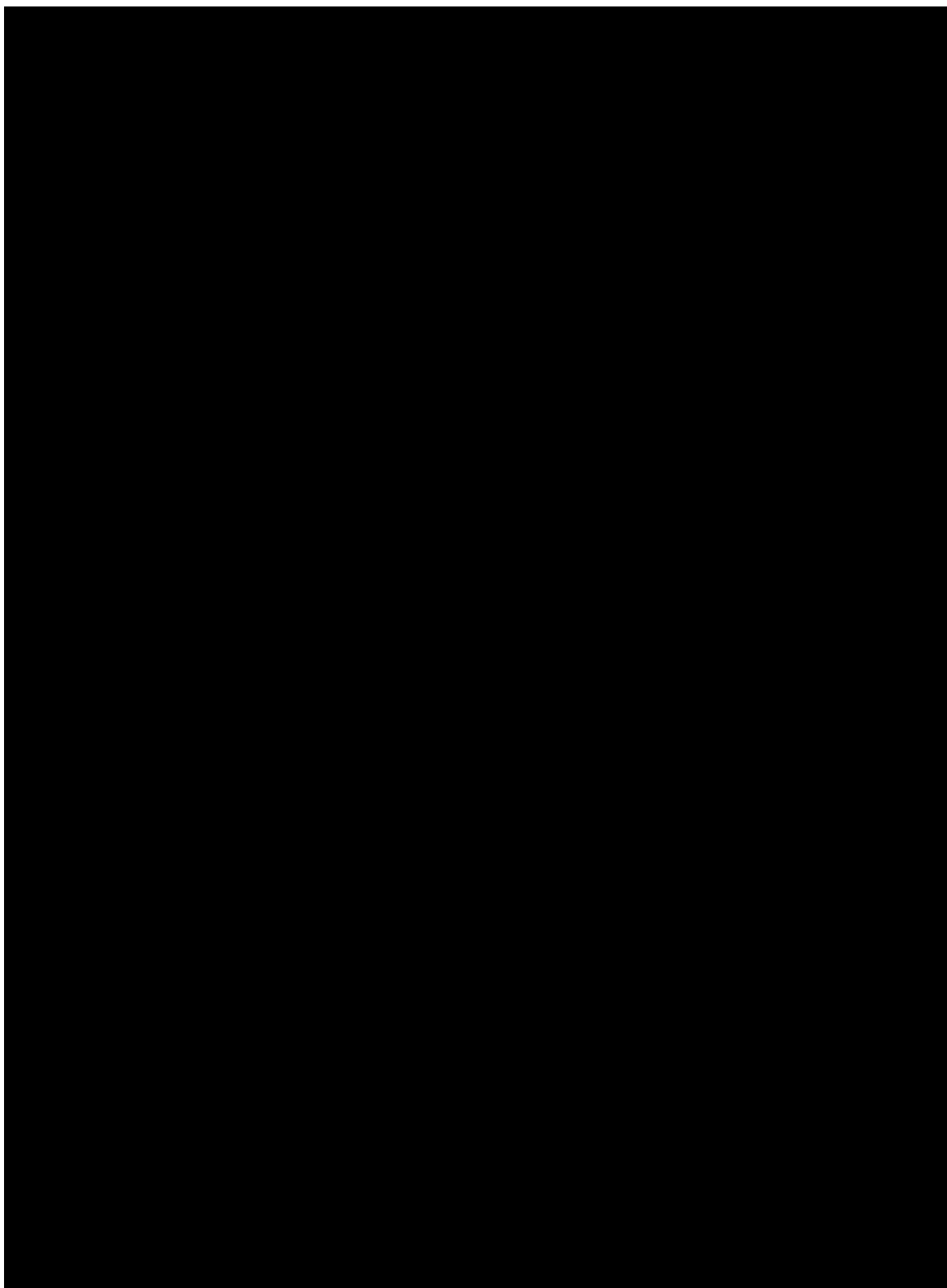
**Appendix 6**  
**Haem-A-QoL (United States/English) (cont.)**



**Appendix 6**  
**Haem-A-QoL (United States/English) (cont.)**



**Appendix 7**  
**EQ-5D-5L (United Kingdom/English)**



**Appendix 7**  
**EQ-5D-5L (United Kingdom/English) (cont.)**

